THE LANCET
Haematology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Diefenbach CS, Hong F, Ambinder RF, et al. Ipilimumab, nivolumab, and brentuximab vedotin combination therapies in patients with relapsed or refractory Hodgkin lymphoma: phase 1 results of an open-label, multicentre, phase 1/2 trial. *Lancet Haematol* 2020; **7:** e660–70.

E4412 Supplemental Materials

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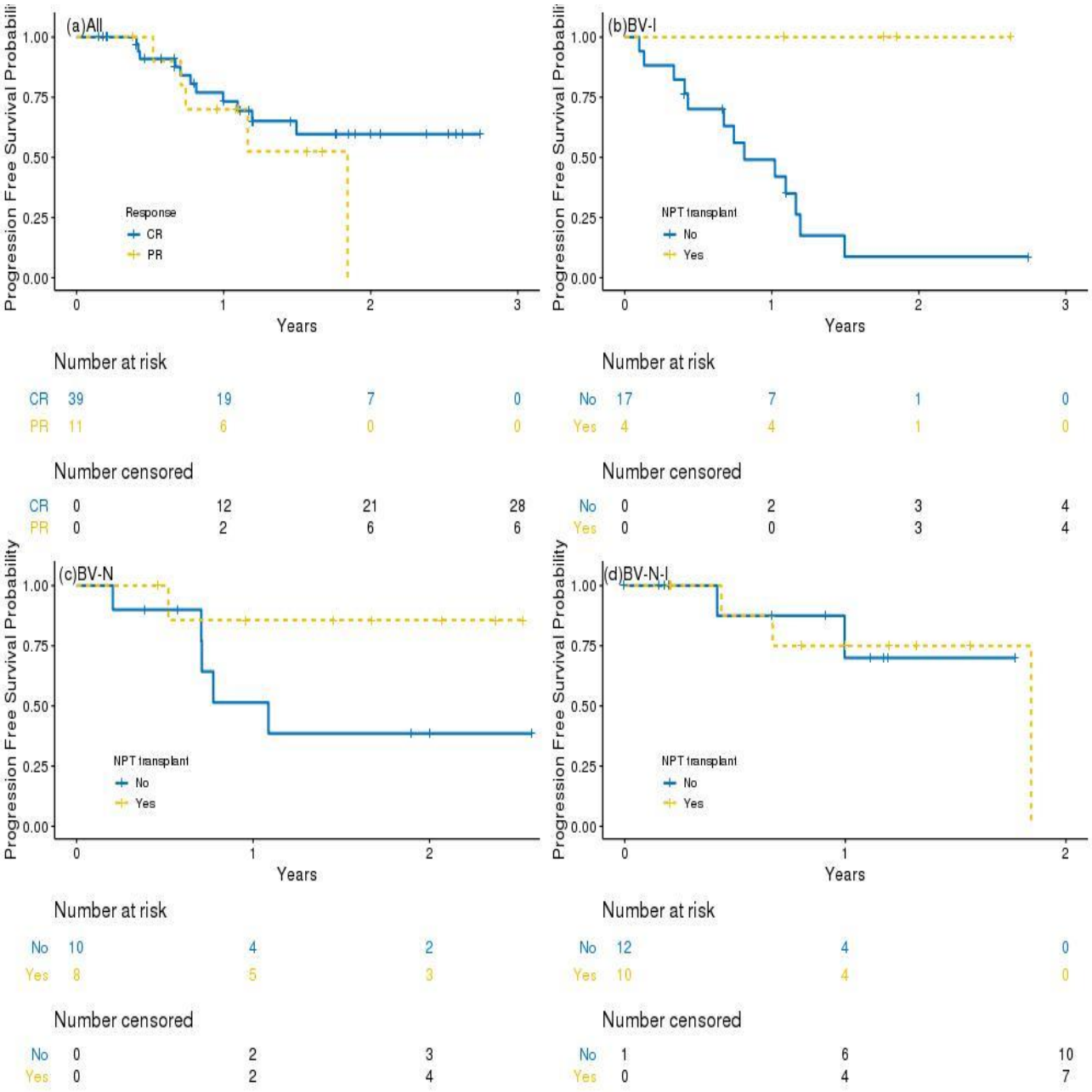

Figure S1: Kaplan Meier estimate of progression free survival (a) by patients with best overall response of complete remission (CR) or partial remission (PR), combining patients treated across all three treatment combinations; by patients who discontinued therapy for HCT versus patients who were post HCT, unfit, or declined HCT: (b) BV-Ipi (B-I) (c) BV-Nivo (B-N); (d) BV-Nivo-Ipi (B-N-I).

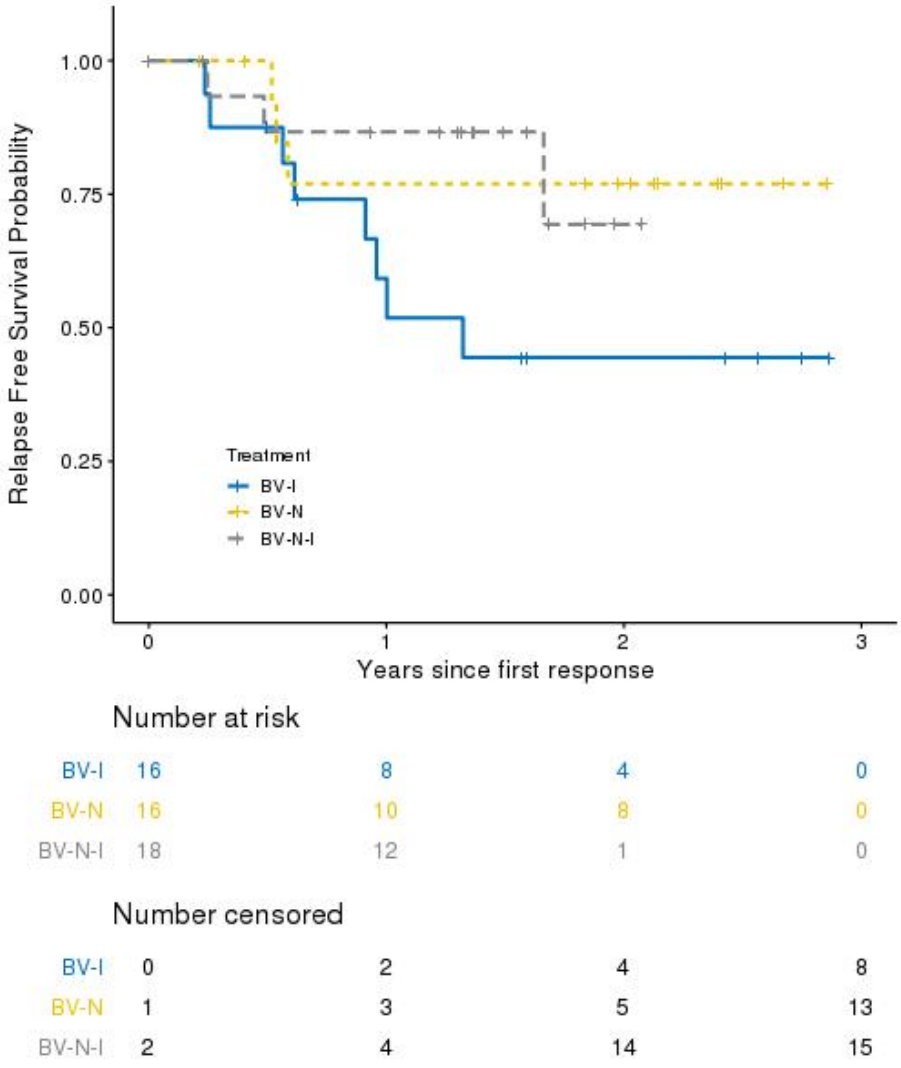

Figure S2: Duration of response (DOR) calculated from the time response was first observed to relapse first observed, and censored at last latest physical examination without sign of progression (the same used in PFS analysis) for BV-Ipi (B-I), BV-Nivo (B-N), and BV-Ipi-Nivo (BV-N-I).

Table S1: Treatment-related toxicity of all grade

Toxicity	Grade										All
	BV-Ipi (n=23)			BV-Nivo (n=19)			BV-Nivo-Ipi (n=22)				
	1, 2	3	4	1, 2	3	5	1, 2	3	4	5	
	N	N	N	N	N	N	N	N	N	N	N
Abdominal pain	3	0	0	0	0	0	5	0	0	0	8
Activated partial thromboplastin time prolonged	0	0	0	0	0	0	1	0	0	0	1
Acute kidney injury	0	0	0	0	0	0	1	0	0	0	1
Alanine aminotransferase increased	11	0	0	9	0	0	2	1	0	0	23
Alkaline phosphatase increased	1	0	0	3	0	0	0	0	0	0	4
Allergic reaction	1	1	0	2	0	0	2	0	0	0	6
Allergic rhinitis	0	0	0	1	0	0	0	0	0	0	1
Alopecia	4	0	0	0	0	0	0	0	0	0	4
Amnesia	0	0	0	1	0	0	0	0	0	0	1
Anemia	5	1	0	9	0	0	7	0	0	0	22
Anorexia	6	0	0	1	0	0	5	0	0	0	12
Arthralgia	3	0	0	1	0	0	2	0	0	0	6
Arthritis	0	0	0	0	0	0	0	1	0	0	1
Aspartate aminotransferase increased	9	0	0	6	0	0	2	1	0	0	18
Ataxia	0	0	0	1	0	0	0	0	0	0	1
Back pain	3	0	0	0	0	0	3	0	0	0	6
Blood and lymphatic system disorders - Other, specify	1	0	0	0	0	0	0	0	0	0	1
Blood bilirubin increased	2	0	0	0	0	0	0	0	0	0	2
Blurred vision	0	0	0	4	0	0	1	0	0	0	5
Bone pain	1	0	0	0	0	0	0	0	0	0	1
Bullous dermatitis	0	0	0	0	0	0	1	0	0	0	1
Chest wall pain	0	0	0	0	0	0	1	0	0	0	1
Chills	3	0	0	1	0	0	4	0	0	0	8
Colitis	0	0	0	0	0	0	0	1	0	0	1
Constipation	3	0	0	0	0	0	2	0	0	0	5
Cough	4	0	0	1	0	0	4	0	0	0	9

Toxicity	Grade										All
	BV-Ipi (n=23)			BV-Nivo (n=19)			BV-Nivo-Ipi (n=22)				
	1, 2	3	4	1, 2	3	5	1, 2	3	4	5	
	N	N	N	N	N	N	N	N	N	N	N
Creatinine increased	1	0	0	0	0	0	2	0	0	0	3
Depression	0	0	0	0	0	0	1	0	0	0	1
Diarrhea	13	1	0	4	0	0	9	1	0	0	28
Dizziness	1	0	0	3	0	0	0	0	0	0	4
Dry eye	2	0	0	0	0	0	2	0	0	0	4
Dry mouth	0	0	0	0	0	0	1	0	0	0	1
Dry skin	2	0	0	0	0	0	2	0	0	0	4
Dysgeusia	0	0	0	0	0	0	2	0	0	0	2
Dyspepsia	3	0	0	1	0	0	0	0	0	0	4
Dysphagia	1	0	0	0	0	0	1	0	0	0	2
Dyspnea	3	0	0	0	1	0	1	0	0	1	6
Edema face	1	0	0	0	0	0	0	0	0	0	1
Edema limbs	3	0	0	1	0	0	0	0	0	0	4
Endocrine disorders - Other, specify	0	0	0	0	0	0	0	0	1	0	1
Eye disorders - Other, specify	2	0	0	2	0	0	1	0	0	0	5
Eye pain	1	0	0	0	0	0	0	0	0	0	1
Fatigue	13	0	0	5	0	0	8	2	0	0	28
Fever	6	0	0	6	0	0	4	0	0	0	16
Flatulence	1	0	0	0	0	0	1	0	0	0	2
Flushing	1	0	0	1	0	0	0	0	0	0	2
Gastritis	0	0	0	0	0	0	1	1	0	0	2
Gastroesophageal reflux disease	1	0	0	0	0	0	0	0	0	0	1
Gastrointestinal disorders - Other, specify	0	0	0	1	0	0	0	0	0	0	1
Gastrointestinal pain	0	0	0	1	0	0	0	0	0	0	1
Gastroparesis	1	0	0	0	0	0	0	0	0	0	1
Headache	6	0	0	6	0	0	5	0	0	0	17
Hiccups	0	0	0	1	0	0	0	0	0	0	1
Hot flashes	0	0	0	1	0	0	0	0	0	0	1
Hypercalcemia	0	0	0	0	0	0	2	0	0	0	2

Toxicity	Grade										All
	BV-Ipi (n=23)			BV-Nivo (n=19)			BV-Nivo-Ipi (n=22)				
	1, 2	3	4	1, 2	3	5	1, 2	3	4	5	
	N	N	N	N	N	N	N	N	N	N	N
Hyperglycemia	0	0	0	3	0	0	1	0	1	0	5
Hyperhidrosis	0	0	0	0	0	0	1	0	0	0	1
Hyperkalemia	0	0	0	0	0	0	0	1	0	0	1
Hypernatremia	0	0	0	1	0	0	0	0	0	0	1
Hypertension	0	1	0	0	0	0	1	0	0	0	2
Hyperthyroidism	0	0	0	0	0	0	1	0	0	0	1
Hyperuricemia	1	0	0	0	0	0	0	0	0	0	1
Hypoalbuminemia	0	0	0	2	0	0	2	0	0	0	4
Hypocalcemia	1	0	0	1	0	0	0	0	0	0	2
Hypoglycemia	1	0	0	0	0	0	0	0	0	0	1
Hypokalemia	2	0	0	1	0	0	1	0	0	0	4
Hyponatremia	0	0	0	2	0	0	0	1	0	0	3
Hypophosphatemia	2	0	0	0	0	0	0	1	0	0	3
Hypotension	0	0	0	0	0	0	1	0	0	0	1
Hypothyroidism	1	0	0	0	0	0	4	0	0	0	5
Hypoxia	0	0	0	0	1	0	0	0	0	0	1
INR increased	0	0	0	0	0	0	1	0	0	0	1
Immune system disorders - Other, specify	0	0	0	0	0	0	1	1	0	0	2
Infusion related reaction	0	0	0	0	0	0	1	0	0	0	1
Insomnia	3	0	0	2	0	0	1	0	0	0	6
Investigations - Other, specify	1	0	0	0	0	0	0	0	0	0	1
Irregular menstruation	1	0	0	0	0	0	0	0	0	0	1
Joint range of motion decreased	1	0	0	0	0	0	0	0	0	0	1
Lipase increased	0	0	0	0	0	0	2	1	1	0	4
Localized edema	0	0	0	1	0	0	0	0	0	0	1
Lymph node pain	0	0	0	1	0	0	0	0	0	0	1
Lymphocyte count decreased	3	0	0	3	0	0	1	1	0	0	8
Malaise	0	0	0	2	0	0	0	0	0	0	2
Mucosal infection	0	0	0	0	0	0	1	0	0	0	1

Toxicity	Grade										All
	BV-Ipi (n=23)			BV-Nivo (n=19)			BV-Nivo-Ipi (n=22)				
	1, 2	3	4	1, 2	3	5	1, 2	3	4	5	
	N	N	N	N	N	N	N	N	N	N	N
Mucositis oral	3	1	0	1	0	0	3	0	0	0	8
Muscle weakness lower limb	0	0	0	0	0	0	1	0	0	0	1
Musculoskeletal and connective tissue disorder - Other, specify	0	0	0	0	0	0	1	0	0	0	1
Myalgia	0	0	0	3	0	0	3	0	0	0	6
Nasal congestion	0	0	0	1	0	0	1	0	0	0	2
Nausea	16	0	0	8	0	0	11	0	0	0	35
Neck edema	1	0	0	0	0	0	0	0	0	0	1
Nervous system disorders - Other, specify	2	0	0	0	0	0	1	0	0	0	3
Neutrophil count decreased	7	0	0	4	1	0	2	0	1	0	15
Non-cardiac chest pain	2	0	0	1	0	0	1	0	0	0	4
Oral dysesthesia	0	0	0	1	0	0	0	0	0	0	1
Pain	7	0	0	5	0	0	7	0	0	0	19
Pain in extremity	1	0	0	0	0	0	1	0	0	0	2
Pancreatitis	0	0	0	0	0	0	0	1	0	0	1
Papulopustular rash	2	0	0	0	0	0	0	0	0	0	2
Paresthesia	1	0	0	0	0	0	1	0	0	0	2
Peripheral motor neuropathy	2	0	0	0	0	0	1	0	0	0	3
Peripheral sensory neuropathy	15	1	0	10	0	0	8	0	0	0	34
Platelet count decreased	1	0	1	4	0	0	5	0	0	0	11
Pneumonitis	1	0	0	0	1	1	1	0	0	0	4
Postnasal drip	0	0	0	0	0	0	1	0	0	0	1
Productive cough	1	0	0	0	0	0	0	0	0	0	1
Pruritus	6	1	0	4	1	0	3	1	0	0	16
Rash acneiform	1	0	0	0	0	0	1	0	0	0	2
Rash maculo-papular	9	5	0	5	1	0	6	2	0	0	28
Respiratory failure	0	0	0	0	0	0	0	0	1	0	1
Respiratory, thoracic and mediastinal disorders - Other, specify	0	0	0	1	0	0	0	0	0	0	1
Restlessness	0	0	0	0	0	0	1	0	0	0	1

Toxicity	Grade										All
	BV-Ipi (n=23)			BV-Nivo (n=19)			BV-Nivo-Ipi (n=22)				
	1, 2	3	4	1, 2	3	5	1, 2	3	4	5	
	N	N	N	N	N	N	N	N	N	N	N
Serum amylase increased	0	0	0	2	0	0	1	1	0	0	4
Sinus tachycardia	0	0	0	1	0	0	1	0	0	0	2
Sinusitis	1	0	0	0	0	0	0	0	0	0	1
Skin and subcutaneous tissue disorders - Other, specify	0	0	0	1	0	0	2	0	0	0	3
Sore throat	2	0	0	0	0	0	1	0	0	0	3
Stevens-Johnson syndrome	0	0	0	0	0	0	0	0	1	0	1
Stomach pain	2	0	0	0	0	0	0	0	0	0	2
Tremor	1	0	0	0	0	0	0	0	0	0	1
Typhlitis	0	0	0	0	1	0	0	0	0	0	1
Upper respiratory infection	1	0	0	1	0	0	0	0	0	0	2
Urinary frequency	0	0	0	0	0	0	1	0	0	0	1
Urinary tract pain	0	0	0	0	0	0	1	0	0	0	1
Uveitis	1	0	0	0	0	0	0	0	0	0	1
Vertigo	1	0	0	0	0	0	0	0	0	0	1
Vomiting	5	1	0	5	0	0	5	2	0	0	18
Weight loss	1	0	0	1	0	0	1	0	0	0	3
Wheezing	0	0	0	1	0	0	0	0	0	0	1
White blood cell decreased	6	0	0	5	0	0	4	2	0	0	17
Worst Toxicity	13	9	1	15	3	1	10	8	3	1	64

Table S2: Number of cases that experienced each type of dose modification (at least on one cycle)

	Treatment			Total
	BV-Ipi (n=23)	BV-Nivo (n=19)	BV-Nivo-Ipi (n=22)	
	N	N	N	N
Ipilimumab				
Dose delayed	2	0	1	3
Dose discontinued	3	0	3	6

	Treatment			Total
	BV-Ipi (n=23)	BV-Nivo (n=19)	BV-Nivo-Ipi (n=22)	
	N	N	N	N
Dose held	5	0	3	8
Dose missed	0	0	1	1
Nivolumab				
Dose delayed	0	2	6	8
Dose escalated	0	1	0	1
Dose held	0	0	2	2
Brentuximab Vedotin				
Dose delayed	6	2	5	13
Dose discontinued	3	1	0	4
Dose held	0	0	1	1
Dose reduced	2	0	3	5
Dose reduced and delayed *	1	1	0	2

*Two cases had "Dose reduced and delayed", none was reported "dose reduced".

Table S3: Grade 3 or higher treatment related toxicity for n=4 cases (1 on BV-Ipi, 2 on BV-Nivo, 1 on BV-Nivo-Ipi) who had prior allogeneic SCT

Toxicity	Grade			All
	BV/Nivo	BV/Nivo/Ipi		
	3	3	4	
	N	N	N	N
Dyspnea	1	0	0	1
Hypoxia	1	0	0	1
Immune system disorders - Other, specify	0	1	0	1
Pneumonitis	1	0	0	1
Pruritus	0	1	0	1
Rash maculo-papular	0	1	0	1
Stevens-Johnson syndrome	0	0	1	1
Typhlitis	1	0	0	1

Toxicity	Grade			All
	BV/Nivo	BV/Nivo/Ipi		
	3	3	4	
	N	N	N	N
Dyspnea	1	0	0	1
Worst Grade	1	0	1	2

Table S4: Grade 3 or higher treatment related toxicity for n=23 cases (9 on BV-Ipi, 6 on BV-Nivo, 8 on BV-Nivo-Ipi) who had prior autologous SCT

Toxicity	Grade					All
	BV/Ipi	BV/Nivo	BV/Nivo/Ipi			
	3	3	3	4	5	
	N	N	N	N	N	N
Alanine aminotransferase increased	0	0	1	0	0	1
Allergic reaction	1	0	0	0	0	1
Aspartate aminotransferase increased	0	0	1	0	0	1
Dyspnea	0	0	0	0	1	1
Fatigue	0	0	1	0	0	1
Gastritis	0	0	1	0	0	1
Hypophosphatemia	0	0	1	0	0	1
Lipase increased	0	0	1	0	0	1
Neutrophil count decreased	0	1	0	1	0	2
Pruritus	0	1	0	0	0	1
Rash maculo-papular	1	1	0	0	0	2
Respiratory failure	0	0	0	1	0	1
Vomiting	0	0	1	0	0	1
White blood cell decreased	0	0	2	0	0	2
Worst Grade	2	2	4	1	1	10

Supplementary APPENDIX: PROTOCOL

List of sites and PIs that accrued patients and numbers of patients accrued*

1) Johns Hopkins University; Richard Ambinder, 13 patients
2) NYU Perlmutter Cancer Center; Catherine Diefenbach, 10 patients
3) Emory University – Winship Cancer Institute; Jonathan Cohen, 8 patients
4) Indiana University School of Medicine; Michael Robertson, 7 patients
5) Rutgers Cancer Institute of New Jersey; Kevin David, 7 patients
6) Stanford Cancer Institute; Ranjana Advani, 5 patients
7) Mayo Clinic; Stephen Ansell, 5 patients
8) Froedtert and the Medical College of Wisconsin; Stefan Fenske, 3 patients
9) Fox Chase Cancer Institute; Stefan Barta, 2 patients
10) Neil Palmisiano; Penn State Milton S Hershey Medical Center, 1 patient
11) Jakub Svoboda, University of Pennsylvania/Abramson Cancer Center, 1 patient
12) David Morgan; Vanderbilt University Medical Center, 1 patient
13) Reem Kamali; Northwestern University/Robert H Lurie Comprehensive Cancer Center, 1 patient.
14) *One additional site did not accrue any patients

A Phase I Study with an Expansion Cohort/Randomized Phase II Study of the Combinations of Ipilimumab, Nivolumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma

STUDY CHAIR: Catherine Diefenbach, M.D.
STUDY CO-CHAIR: Stephen Ansell, M.D., Ph.D
Rev. 9/15
IMAGING CHAIR: Lale Kostakoglu, M.D., M.P.H.
STUDY STATISTICIANS: Fangxin Hong, Ph.D
Opeyemi Jegede, M.S.
IMAGING STATISTICIAN: Fenghai Duan, Ph.D
LYMPHOMA COMMITTEE CHAIR: Brad Kahl, M.D
PATHOLOGY AND LABORATORY CO-CHAIRS: Yasodha Natkunam, M.D.
David Scott, MBChB Ph.D.
Catherine Diefenbach, M.D.
Christian Steidl, M.D.

Version Date: May 22, 2019
NCI Update Date: September 18, 2013

Rev. 8/14

STUDY PARTICIPANTS	***ACTIVATION DATE***	
Phase I - *Limited Institutions:*	Phase I - January 24, 2014	
	Phase II - June 20, 2018	
NY011 / New York University (ECOG-ACRIN)	***PRE-ACTIVATION DATE***	
MN026 / Mayo Clinic, Rochester (ECOG-ACRIN)	September 19, 2013	
CA141 / Stanford (ECOG-ACRIN)	Addendum #1 – Incorporated Prior to Activation	
MD017 / Johns Hopkins (ECOG-ACRIN)	Addendum #2 – Incorporated Prior to Activation	
GA005 / Emory (ECOG-ACRIN)	Update #1 – Incorporated Prior to Activation	
IN007 / Indiana University (ECOG-ACRIN)	Addendum #3 – 5/14	Addendum #17
Rev. 9/15 **WI013 /** Medical College of Wisconsin (ECOG-ACRIN)	Addendum #4 – 8/14	Addendum #18
PA086 / Fox Chase Cancer Center (ECOG-ACRIN)	Addendum #5 – 10/14	Addendum #19
IL036 / Northwestern University (ECOG-ACRIN)	Addendum #6 – 1/15	Addendum #20
NJ066 / Rutgers Cancer Institute (ECOG-ACRIN)	Addendum #7 – 9/15	Addendum #21
MA033 / Tufts Medical Center (ECOG-ACRIN)	Addendum #8 – 9/15	Addendum #22
PA042 / Penn State Milston S Hershey Cancer Center (ECOG-ACRIN)	Addendum #9 – 12/15	
	Addendum #10 – 3/16	
TN008 / Vanderbilt University (ECOG-ACRIN)	Addendum #11 – 9/16	
Rev. 9/16 **PA075 /** University of Pennsylvania (ECOG-ACRIN)	Addendum #12 – 11/16	
Phase II *– US Sites only*	Addendum #13 – 2/17	
ALLIANCE / Alliance for Clinical Trials in Oncology	Addendum #14 – 5/17	
Rev. Add16 **NRG** / NRG Oncology	Addendum #15 – 11/17	
SWOG / SWOG	Addendum #16	

Rev. Add20 ***NCTN GROUP STUDY CHAMPIONS:***
ALLIANCE: Neha Mehta-Shah, MD
SWOG: Jennifer Amengual, MD

Agents	**IND#**	**NSC#**	**Supply**	**IND Sponsor**
Ipilimumab (BMS-734016, MDX-010)	133111	NSC 732442	NCI-Supplied	DCTD, NCI
Brentuximab Vedotin		NSC 749710	Commercial	Commercially Available
Rev. Add19 Nivolumab (BMS-936558, MDX-1106, and ONO-4538)		NSC 748726	NCI-Supplied	DCTD, NCI

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Rev. Add20

STUDY CHAIR

Catherine Diefenbach, M.D.
NYU Perlmutter Cancer Center
240 East 38th Street
19th Floor
New York, NY 10016
Phone: 212-731-5670
Fax: 212-731-5540
Email: Catherine.Diefenbach@nyumc.org

STUDY CO-CHAIR

Stephen Ansell, M.D., Ph.D
Mayo Clinic
200 First Street S.W.
Rochester, MN 55905
Phone: 507-284-0923
Fax: 507-266-4972
Email: Ansell.stephen@mayo.edu

STUDY CHAIR LIAISON (SCL)

Samantha Lowenkron
New York University
1 Park Avenue, Mezzanine Level
New York, NY 10016
Phone: 929-455-2428
Fax: 929-455-2490
Email:
Samantha.Lowenkron@nyulangone.org

SWOG STUDY CHAMPION

Jennifer Amengual, MD
Columbia University Medical Center
51 West 51st Street Suite 200
New York, NY 10019
Phone: 212-326-5720
Fax: 212-326-5725
Email: jea2149@columbia.edu

ALLIANCE STUDY CHAMPION

Neha Mehta-Shah, MD
Washington University School of Medicine
660 South Euclid Avenue, Campus Box 8056
Saint Louis, MO 62110
Phone: 314-747-7402
Fax: 314-747-5123
Email: Mehta-n@wustl.edu

Rev. 8/14	***INSTITUTION CONTACT INFORMATION***		
	New York University		
Rev. Add16 Rev. Add20	Investigator: Catherine Diefenbach, MD Nurse/CRA: Samantha Lowenkron	Phone: 212-731-5670 Phone: 929-455-2428	Email: Catherine.Diefenbach@nyumc.org Email: samantha.lowenkron@nyulangone.org
	Mayo Clinic, Rochester		
	Investigator: Stephen Ansell, MD, PhD Nurse/CRA: Tamera J. Simmons	Phone: 507-284-0923 Phone: 507-284-4740	Email: Ansell.stephen@mayo.edu Email: Simmons.Tamera@mayo.edu
	Stanford		
Rev. 5/14, Add16	Investigator: Dr Ranjana Advani, MD Nurse/CRA: Won W. Chang	Phone: 650-725-6456 Phone: 650-736-8113	Email: radvani@stanford.edu Email: w4chang@standford.edu
	Emory		
Rev. 5/14, Add16	Investigator: Jonathon B Cohen, MD, MS Nurse/CRA: Ashley Archer	Phone: 404-778-2214 Phone: 404-778-8641	Email: jonathon.cohen@emory.edu Email: asarche@emory.edu
	Johns Hopkins		
	Investigator: Richard Ambinder, MD, PhD Nurse/CRA: Judy Murray	Phone: 410-955-8839 Phone: 410-955-4044	Email: rambind1@jhmi.edu Email: jmurra33@jhmi.edu
	Indiana University		
Rev. 9/15	Investigator: Michael Robertson, MD Nurse/CRA: Jill Weisenbach, RN, BSN	Phone: 317- 278-6942 Phone: 317-278-0597	Email: mjrobert@iu.edu Email: jweisenb@iupui.edu
	Medical College of Wisconsin		
	Investigator: Timothy Fenske, MD Nurse/CRA: Arielle Baim	Phone: 414-805-4633 Phone: 414-805-8745	Email: tfenske@mcw.edu Email: abaim@mcw.edu
Rev. 9/15	**Fox Chase Cancer Center**		
	Investigator: Stefan K. Barta, MD, MS, MRCP (UK) Nurse/CRA: April King, MS	Phone: 215-728-2674 Phone: 215-214-0306	Email: stefan.barta@fccc.edu Email: april.king@fccc.edu
	Northwestern University		
	Investigator: Leo I Gordon, MD, FACP Nurse/CRA: Jose D. Zavala, MBA, CCRC	Phone: 312-695-4546 Phone: 312-695-1377	Email: ~~l-gordon@northwestern.edu~~ Email: ~~jose.zavala@northwestern.edu~~

Rev. 8/14

INSTITUTION CONTACT INFORMATION		
Rutgers Cancer Institute		
Investigator: Kevin David, MD Nurse/CRA: Nora Barboza	Phone: 732-235-2045 Phone: 732-235-5972	Email: davidka@cinj.rutgers.edu Email: nb395@cinj.rutgers.edu
Tufts Medical Center		
Investigator: Andrew Evens, DO, MSc, FACP Nurse/CRA: Elizabeth Kendricken, RN, BSN	Phone: 617-636-0227 Phone: 617-636-5558	Email: aevens@tuftsmedicalcenter.org Email: ekendricken@tuftsmedicalcenter.org
Penn State Milton S Hershey Cancer Center		
Investigator: Neil Palmisiano, MD Nurse/CRA: Lea May, BSN, RN, OCN	Phone: 717-531-0003 Phone: 717-531-0003	Email: npalmisiano@hmc.psu.edu Email: lmay1@hmc.psu.edu
Vanderbilt University		
Investigator: David Morgan, MD Nurse/CRA: Deborah.Sutherland@Vanderbilt.edu	Phone: 615-936-8422 Phone: 615-875-9884	Email: david.morgan@vanderbilt.edu Email: deborah.sutherland@vanderbilt.edu
University of Pennsylvania		
Investigator: Jakub Svoboda, MD Nurse/CRA: Terease Waite, MS, RN, JD, MBE	Phone: 215-614-1846 Phone: 267-324-8497	Email: jakub.svoboda@uphs.upenn.edu Email: terese.waite@uphs.upenn.edu

Rev. Add16

Rev. Add16

Rev. 9/16

<table>
<tr><th colspan="3">CONTACT INFORMATION</th></tr>
<tr><th>For regulatory requirements:</th><th>For patient enrollments:</th><th>For study data submission:</th></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.

Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.)

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.

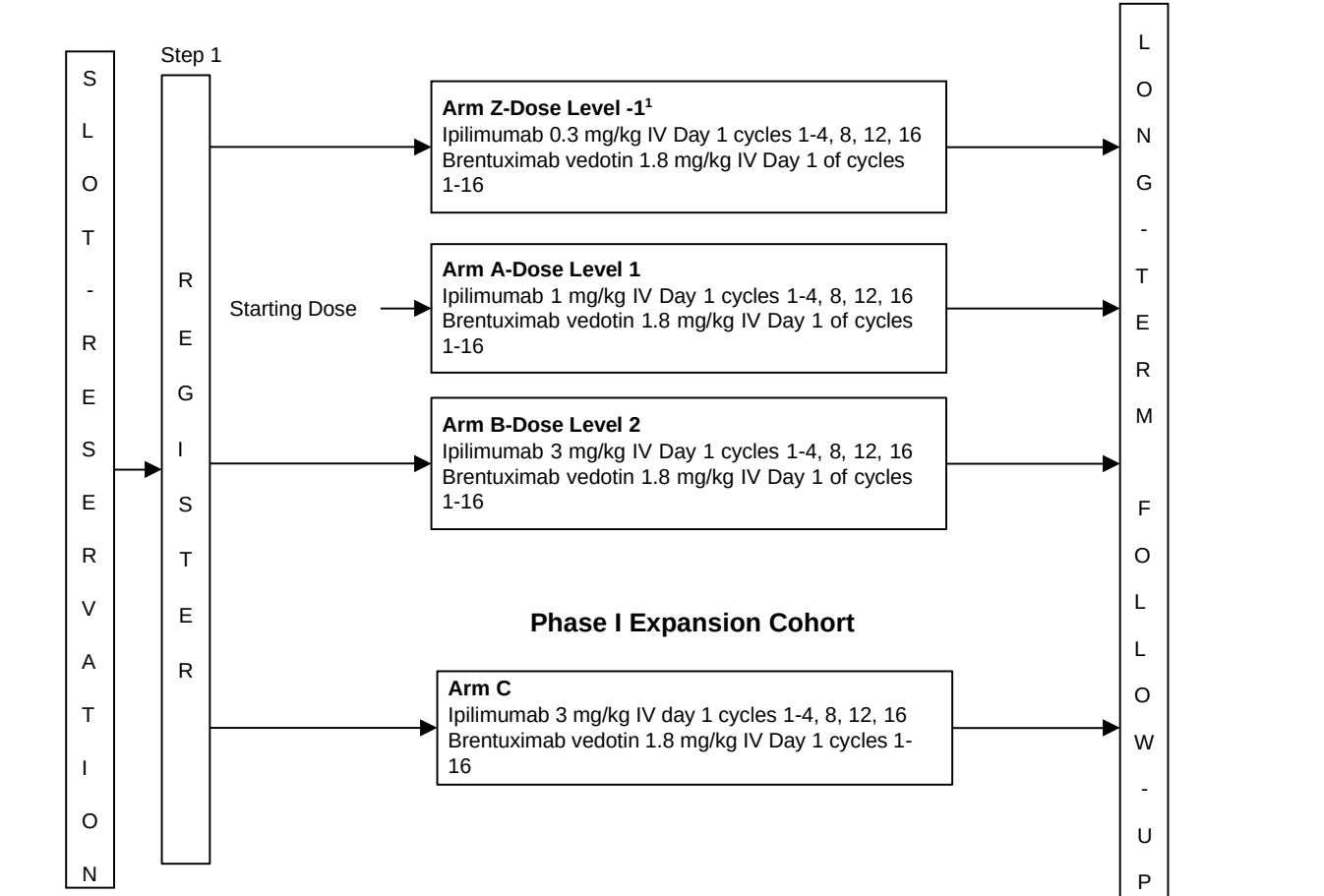
Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</td><td>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.

Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.</td><td>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.</td></tr>
<tr><td colspan="3"><u>For clinical questions (i.e. patient eligibility or treatment-related):</u> contact the Study PI of the Lead Protocol Organization.</td></tr>
<tr><td colspan="3"><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or e-mail:

CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
<tr><td colspan="3">The CTSU Website is located at https://www.ctsu.org.</td></tr>
</table>

Rev. 1/15, 9/15

Schema – Brentuximab Vedotin + Ipilimumab
Phase I Dose Escalation (closed to accrual)



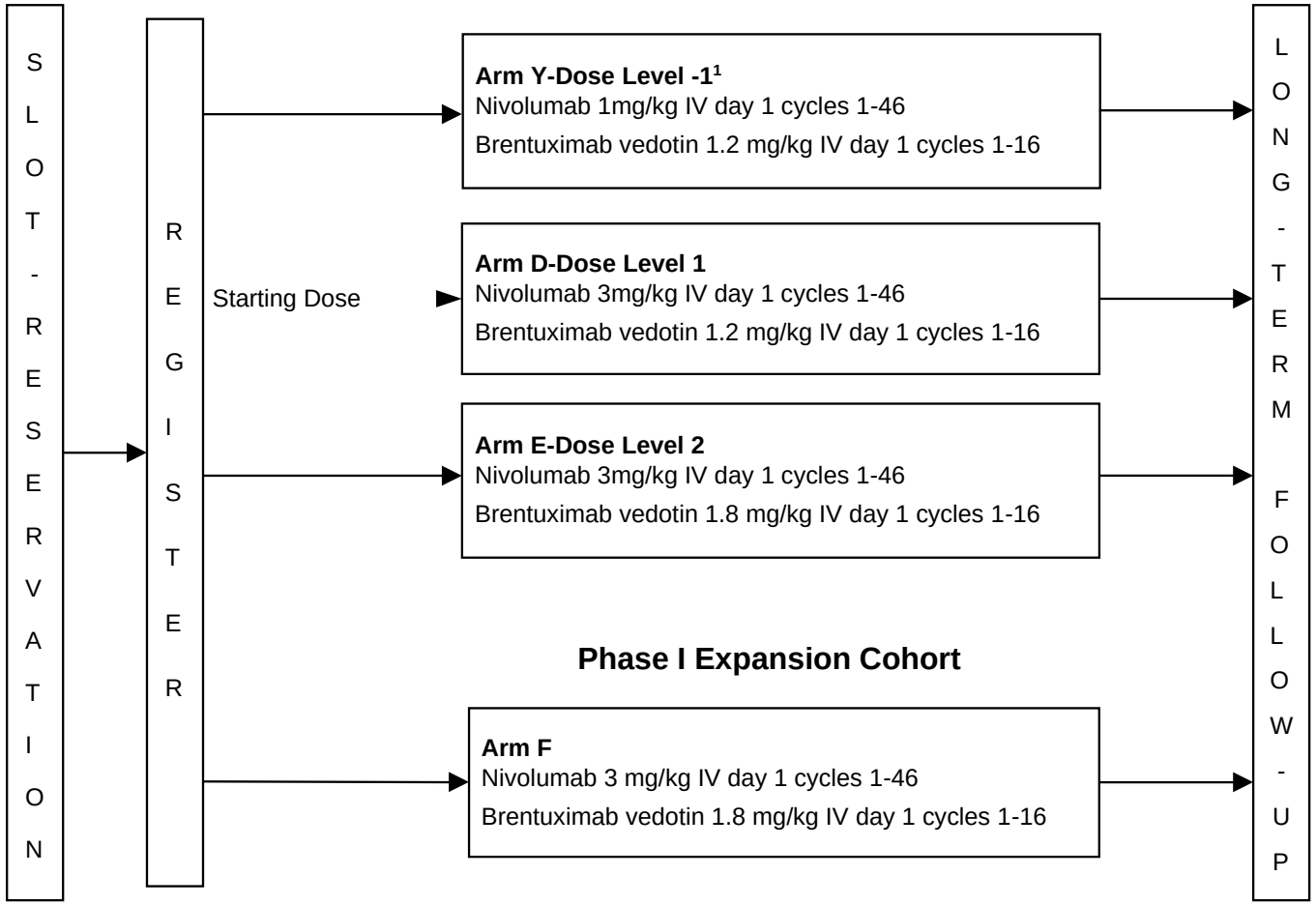
Cycle = 21 days

Phase I Dose Escalation Accrual Goal: 6-18 patients
Phase I Expansion Cohort Accrual goal: 9 patients

1. Arm Z Dose Level -1 will only open if significant toxicity is experienced on Arm A and dose de-escalation is required. Refer to Section 5.

Rev. 1/15, 9/15, 11/16, Add16

Schema – Brentuximab Vedotin + Nivolumab
Phase I Dose Escalation (closed to accrual)

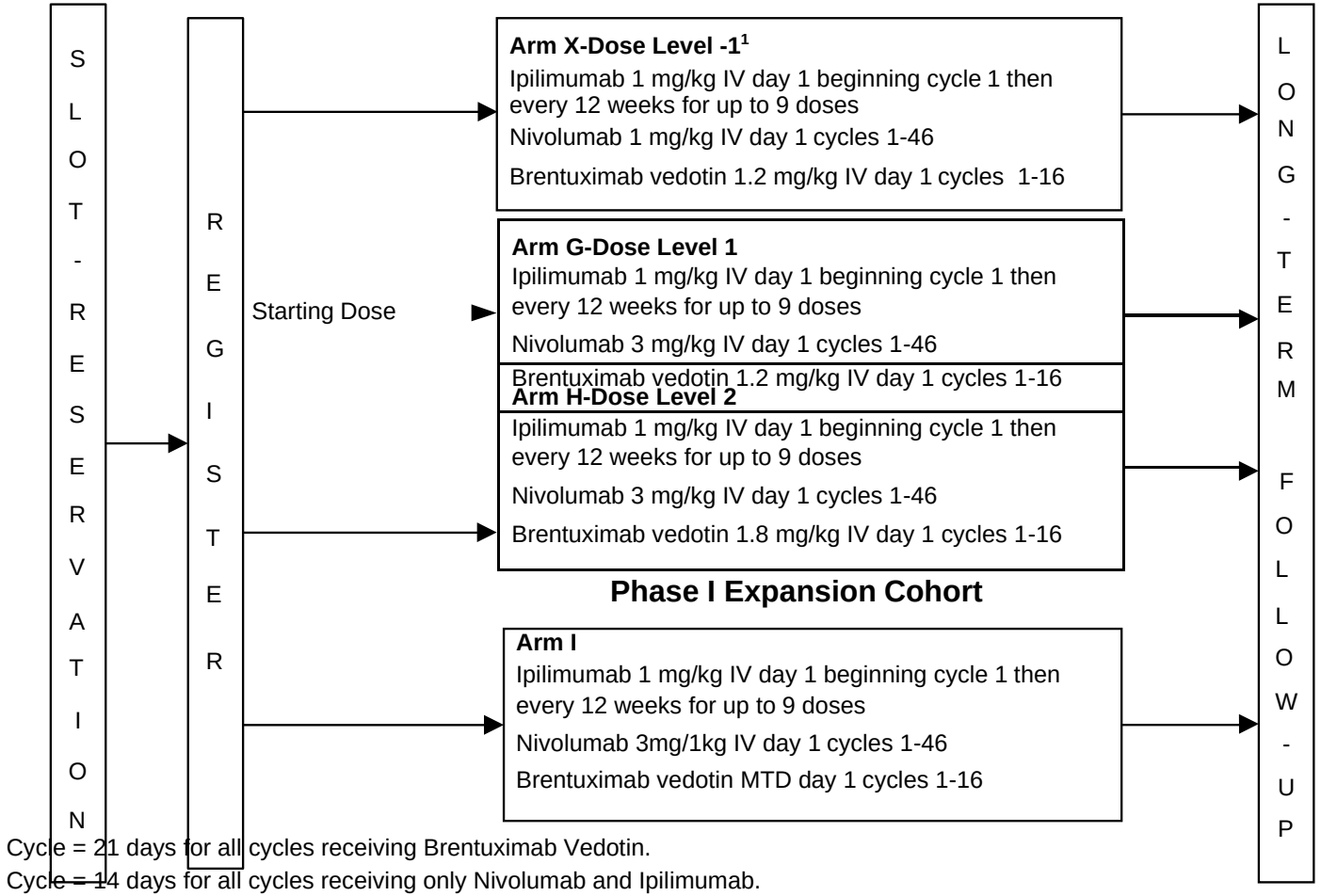


Cycle = 21 days for all cycles receiving Brentuximab Vedotin.
Cycle = 14 days for all cycles receiving only Nivolumab.

1. Arm Y Dose Level -1 will only open if significant toxicity is experienced on Arm D and dose de-escalation is required. Refer to Section 5.

Rev. 9/15, 5/17, 11/17

Schema – Brentuximab Vedotin + Nivolumab + Ipilimumab
Phase I Dose Escalation (closed to accrual)

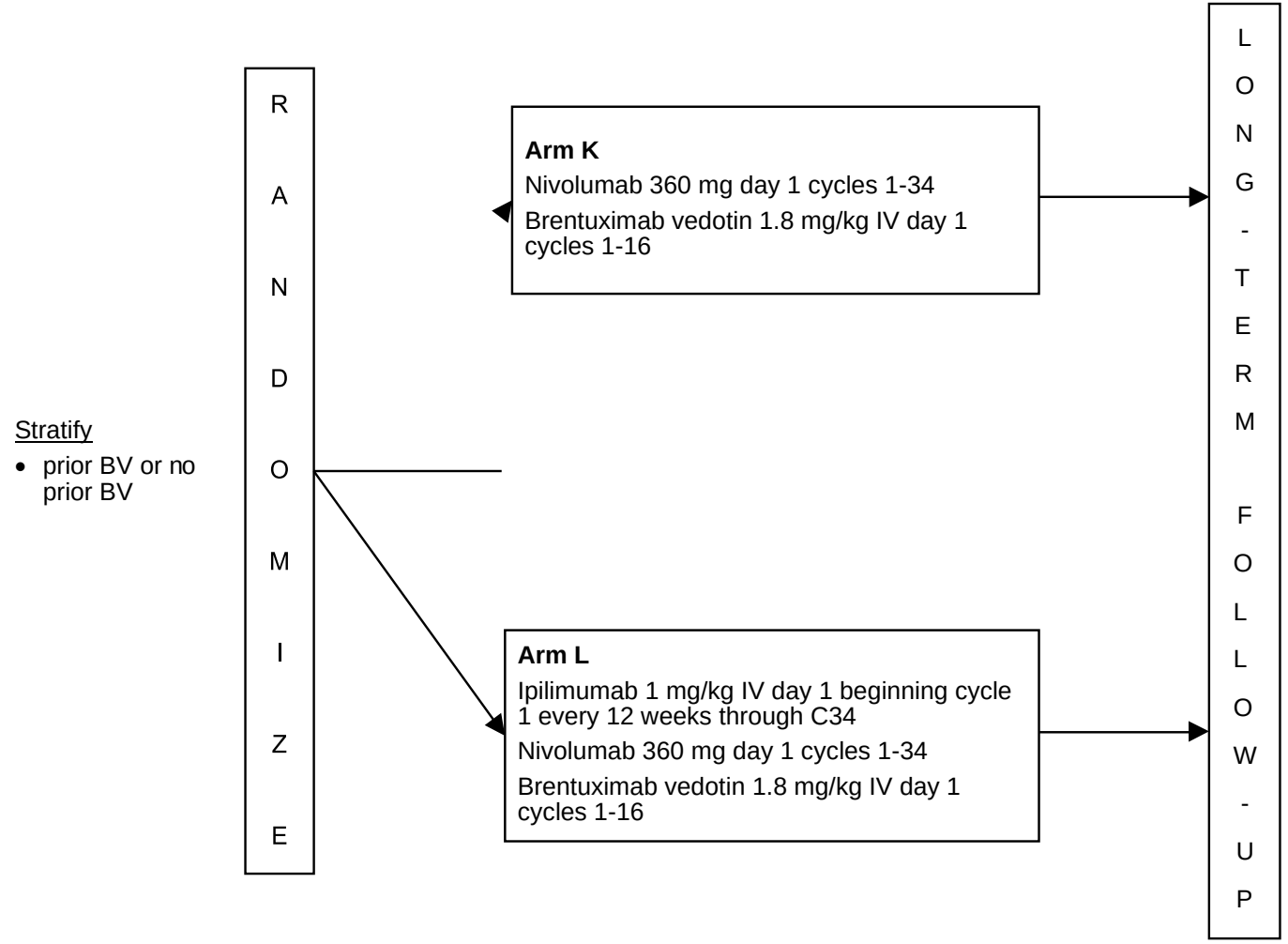


Cycle = 21 days for all cycles receiving Brentuximab Vedotin.
Cycle = 14 days for all cycles receiving only Nivolumab and Ipilimumab.

1. Arm X Dose Level -1 will only open if significant toxicity is experienced on Arm G and dose de-escalation is required. Refer to Section 5.

Rev. Add16

Schema – Phase II



Phase II Accrual Goal=120 patients
Cycle=21 days

Rev. 1/15

1. Introduction

1.1 Hodgkin Lymphoma

Hodgkin Lymphoma (HL) is a B cell lymphoid neoplasm, which accounts for approximately 10% of all lymphomas diagnosed in the developed world annually. In 2009, approximately 8500 cases of HL were diagnosed in the US (1). The median age at diagnosis is 38 years of age, and at least 40% of patients are under age 35 at the time of diagnosis (2). Over the past 30 years advances in the therapy of HL have led to successful clinical outcomes, with roughly 70% of patients cured with chemotherapy or combined modality therapy. Despite this high cure rate, approximately 5-10% of patients have primary refractory disease, and 20–30% of patients will experience relapse after attaining initial complete remission. Second-line chemotherapy and autologous stem cell transplant (ASCT) approaches are curative for only 50% of patients with relapsed/refractory disease. Maximal cytoreduction prior to SCT confers the greatest potential benefit, yet the current standard salvage chemotherapy regimens such as ICE (ifosfamide, cyclophosphamide, and etoposide) or brentuximab vedotin have a low complete response (CR) rate despite a high overall response rate (ORR) (3, 4) For patients who relapse after ASCT the median time-to-progression with subsequent therapy is reported to be 3.8 months, and median survival is 26 months (5, 6). Allogeneic stem cell transplantation (alloSCT) can induce durable remissions in some patients with relapsed and primary refractory HL; however the use of this modality is limited in part by the challenges of achieving adequate disease control prior to transplantation. Despite the successes associated with modern management of HL, there remain an estimated 1300 deaths annually from HL in the US (7), many of whom are young adults. Improving the CR rate may allow more of these patients to proceed to successful transplantation. For the patient who fails SCT, the emergence of promising new therapies represent highly active alternatives to standard chemotherapy. The identification of active novel combinations which can deepen CR rates, and prolong response rates for these patients remains a major treatment goal and challenge.

1.2 The Role of the Tumor Microenvironment in Hodgkin Lymphoma

Pathologically, HL is a lymphoid neoplasm, characterized by the presence of large binucleated or multinucleated cells with prominent nucleoli termed Hodgkin/Reed Sternberg cells (HRS cells). Immunostains are characteristically positive for CD15 and CD30, and this pattern confirms diagnosis. The malignant HRS cells, which comprise a small fraction (0.1–10%) of the total cellular population, reside in a milieu of reactive inflammatory cells which produce soluble and membrane-bound factors that promote HRS cell growth, evasion of self-immunity, and survival (8-11). HRS cells orchestrate their microenvironment to avoid immune attack by suppressing anti-tumor immune surveillance (12). Over-expression by the HRS cells of surface molecules such as Fas ligand, which induces apoptosis in tumor specific cytotoxic lymphocytes (CTLs), and galectin-1 which is correlated with decreased infiltration of CD8+ effector cells at the tumor site, maintain peripheral tolerance (13-18). Up-regulation of the receptor programmed death ligand-1 (PDL-1) on HRS cells induces anergy in peri-tumoral T cells (19, 20). The T cell exhaustion and deficient anti-tumor immunity induced by the HRS cells within their microenvironment play a key role

in creating and propagating a permissive milieu for HL growth.The negative impact of the tumor microenvironment on clinical outcome has been well established in HL and in other lymphomas (10, 21, 22). Lack of HLA class II expression by HL on the surface of HRS cells is correlated with reduced immunogenicity, and associated with adverse clinical outcome (23) . Gene expression profiling in HL patients has demonstrated a tumor tissue signature of monocytes and tumor-associated macrophages that is associated with relapsed/ refractory disease or inferior clinical outcome. Increased numbers of CD68+ macrophages in the affected lymph nodes of HL patients have been associated with inferior disease specific survival (24).

1.3 Dysfunctional T Cells in Hodgkin Lymphoma

T cells are the most abundant cells in the HL microenvironment (25), and are dysfunctional, demonstrating anergy to recall antigen when stimulated (26). Anergic T cells are unable to recognize and clear foreign cells, including HRS tumor cells. This T cell dysfunctionality is further evidence of the impact of the HRS cells on their microenvironment. The primary phenotype of the T cells in closest proximity to the HRS cells appears to be T helper T (Th2) and T regulatory (Treg) cells (26, 27). There is a paucity of Th1 effector T cells, and cytotoxic T cells. The significance of regulatory T cell subsets (Tr1 and Tr3) in the HL microenvironment is becoming increasingly clear. Prior description of the intra-tumoral milieu in HL as predominantly Th2 in phenotype is overly simplistic. While there are very little Th1 characteristics among the HL infiltrating lymphocytes (HLILs), Th2 features are also sparse. Moreover, although IL-10 is clearly secreted, secretion of IL-4 and IL-13 (common Th2 cytokines) are not seen. IL-10 in the absence of IL-4 is recognized as a marker for regulatory (Tr1) T cells. The HRS cells themselves appear to play a key role in suppressing the cytotoxic activity of the T cells in the tumor microenvironment. The HRS cells secrete cytokines such as Tarc (CCL17), CCL5,and CCL22 attracting Th2 and Treg cells, and the interleukin IL-7, which induces differentiation of naïve CD4+ T cells towards FoxP3+ Treg cells (28-31). The galectin-1 expressed on the surface of HRS cells (17) in co-culture experiments with activated T cells and HL cells lines induced secretion of Th2 cytokines and expansion of T reg cells; knockdown of galectin-1 increased overall viability and restored the Th1/Th2 balance (18). Three potential complementary mechanisms of HLIL suppression have been described: IL-10 secretion, cell-cell contact, and engagement of CTLA-4 (32). All 3 mechanisms have been confirmed as contributing to the regulatory activity of the HLILs; there is variability between patients as to which of these mechanisms predominates (32). Relapsed and refractory HL cannot be cured with conventional chemotherapy and it is a widely accepted concept that the crosstalk between HRS cell and tumor microenvironment has adapted and evolved under the selection pressure of chemotherapies to generate resistance to standard therapies. Therefore any therapeutic strategy which definitively targets relapsed/refractory HL will ideally need to target both components of the lymphoma: depleting the malignant HRS cells which propagate and maintain the dysfunctional tumor microenvironment, and activating the anergic cells of the tumor microenvironment to enhance their ability to recognize and kill the HRS cells. Novel immunotherapies in combination with existing chemotherapy strategies which address this problem are needed.

1.4 Ipilimumab: A Tumor Microenvironment Targeting Strategy

1.4.1 Mechanism of Action

Advances in the understanding of the molecular mechanisms regulating T cell activation have suggested novel strategies for cancer immunotherapy. Optimal activation of naïve T cells requires both the ligation of T cell antigen receptor peptide/MHC complexes, and confirmatory co-stimulatory signals mediated by engagement of CD28 on T cells by B7 molecules expressed on the surface of antigen presenting cells (APCs) (33). The interaction of CD28 with B7 induces T cell proliferation, cytokine secretion, and enhances effector T cell functions. Cytotoxic T lymphocyte antigen 4 (CTLA-4) is a crucial component of the counter-regulatory circuit that inhibits T cell activation. CTLA-4 is upregulated on the T cell surface following activation, and binds with higher avidity to both CD80 and CD86 then CD28 does, thereby delivering negative regulatory signals to T cells (34). CD28 and CTLA-4 have opposing effects in modulating the threshold for T cell activation, and the effector immune response (35, 36). Antibody blockade of CTLA-4-B7 interaction while preserving signaling via CD28 resulted in enhanced T cell responses *in vitro* (35, 37-40) similarly cross-linking of CTLA-4 with CD3 and CD28 inhibits T cell responses (35). Further support for the observation that CTLA-4 functions as a negative regulator of the T cell response is demonstrated by the fact that CLTA-4 deficient mice develop a fatal lymphoproliferative disorder (39, 41-43).

The expression of B7 is restricted to a small group of specialized hematopoeitic APCs, primarily dendritic cells, activated macrophages, and activated B cells. This narrow range ensures that T cell activation can only be stimulated by the appropriate APCs under the correct conditions, maintaining peripheral T cell tolerance (44). Most tumor cells do not express B7 on their surface, it is likely that this contributes to their poor capacity to elicit immune responses (45, 46). Blockade of CTLA-4 with monoclonal antibodies enhances T cell responses, and induces anti-tumor immunity in murine model systems of multiple solid tumors (47-52) The efficacy of CTLA-4 in these model systems appeared to correlate with the inherent immunogenicity of the tumor, however combination therapy with chemotherapy, tumor vaccines, or debulking surgery demonstrated enhanced efficacy even in poorly immunogenic tumors (53-57) .

1.4.2 Preclinical Data for Ipilimumab

Ipilimumab has specificity and a high affinity for human CTLA-4. The calculated dissociation constant (KD) value from an average of several studies was 5.25 nM. Binding of ipilimumab to purified, recombinant human CTLA-4 antigen was also demonstrated by enzyme-linked immunosorbent assay (ELISA) with half-maximal binding at 15 ng/mL, whereas saturation was observed at approximately 0.1 µg/mL. No cross-reactivity was observed against human CD28. Ipilimumab completely blocked binding of B7.1 and

B7.2 to human CTLA-4 at concentrations higher than 6 µg/mL and 1 µg/mL, respectively.

A series of *in vitro* experiments was performed to assess the ability of ipilimumab to induce complement-dependent cellular cytotoxicity (CDCC) or antibody-dependent cellular cytotoxicity (ADCC) *in vitro*. Data suggest that treatment with ipilimumab has a low ability to elicit effector functions able to deplete activated T cells in vivo. Since ipilimumab does not cross-react with mouse CTLA-4, pharmacology studies with ipilimumab in rodents could not be performed. Therefore, a transgenic mouse line was developed to express human, but not murine, CTLA-4 (human CTLA-4 C57BL/6 murine CTLA-4-/-). Efficacy studies conducted in human CTLA-4 transgenic mice implanted with the poorly immunogenic colon tumor line MC 38 showed that multiple doses of ipilimumab produced tumor rejection in 10% to 50% of mice or delay in tumor growth.

Since ipilimumab recognizes CTLA-4 expressed on activated cynomolgus monkey T cells, pharmacology studies were conducted in this animal species to determine the effect of ipilimumab on immune responses to T-cell dependent antigens. In these studies, significant enhancement of the antibody response to the test antigens was observed compared to the response of animals treated with a control antibody or vehicle ($P < 0.05$).

1.4.3 Clinical Safety Data for Ipilimumab

Ipilimumab (NSC732442) has been investigated in over ~10,000 subjects in several cancer types including: melanoma, prostate, and lung cancer, as well as a compassionate use program. Ipilimumab is currently being investigated both as a monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies. Phase 3 programs are ongoing in melanoma and prostate cancer and lung cancer. In melanoma, 2 completed Phase 3 studies (MDX010-20 and CA184024) have demonstrated a clinically meaningful and statistically significant survival benefit in pretreated advanced melanoma and previously untreated advanced melanoma, respectively.

The safety profile of ipilimumab is generally consistent across all clinical trials with the majority of adverse events inflammatory in nature, most commonly fatigue, diarrhea, pruritis, rash, and colitis. The majority of these events were manageable with immune suppressive therapies. MDX010-20 was a randomized, double-blind clinical study that evaluated exposure to ipilimumab at 3 mg/kg for four doses given by intravenous infusion in patients with unresectable or metastatic melanoma. The patients in the study received a median of 4 doses of ipilimumab (range 1 to 4 doses). Ipilimumab was discontinued for adverse reactions in 10% of patients, with the most common adverse reactions (≥ 5%) fatigue, diarrhea, pruritus, rash, and colitis. Table 1 presents selected adverse reactions from MDX010-20, which occurred in at least 5% of patients in the ipilimumab-containing arms and with at least 5% increased incidence

over the control gp100 arm for all-grade events and at least 1% incidence over the control group for Grade 3–5 events. In MDX010-20, immune related adverse events (irAEs) occurred in 60% of subjects treated with an ipilimumab (3mg/kg) containing regimen; ≥ Grade 3 events in 12-16%. Rates for subcategories of irAEs varied by the organ system involved, with skin and GI events occurring more frequently than endocrine, hepatic and other events.

Table 1: Selected Adverse Reactions in MDX010-20 at 3mg/kg

	Percentage (%) of Patients[a]					
	YERVOY 3 mg/kg n = 131		YERVOY 3mg/kg + gp100 n = 380		gp100 n = 132	
System Organ Class/Preferred Term	Any Grade	Grade 3-5	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Gastrointestinal Disorders						
Diarrhea	32	5	37	4	20	1
Colitis	8	5	5	3	2	0
Skin and Subcutaneous Tissue Disorders						
Pruritus	31	0	21	<1	11	0
Rash	29	2	25	2	8	0
General Disorders and Administration Site Conditions						
Fatigue	41	7	34	5	31	3

a 1 (0.4%) hypophysitis was reported on Day 364.

Table 2 presents the per-patient incidence of severe, life-threatening, or fatal immune-mediated adverse reactions from MDX010-20.

Table 2: Severe to Fatal Immune-mediated Adverse Reactions in MDX010-20

	Percentage (%) of Patients	
	YERVOY 3 mg/kg n = 131	YERVOY 3 mg/kg + gp100 n = 380
Any Immune-mediated Adverse Reaction	15	12
Entercolitis [a,b]	7	7
Hepatotoxicity [a]	1	2
Dermatitis [a]	2	3
Neuropathy [a]	1	< 1
Endocrinopathy	4	1
Hypopituitarism	4	1
Adrenal insufficiency	0	1
Other		
Pneumonitis	0	< 1
Meningitis	0	< 1
Nephritis	1	0
Eosinophilia [c]	1	0
Pericarditis [a,c]	0	< 1

1.4.4 Management of Adverse Events

The early diagnosis of inflammatory events and immune related AEs is important to initiate therapy and minimize complications. Inflammatory events are generally manageable using symptomatic or immuno-suppressive therapy as recommended through detailed diagnosis and management guidelines as described in Section 5.9.1 and in the appendices.

A program-wide independent data monitoring committee (DMC) reviews data from the ipilimumab studies, allowing for an ongoing safety and benefit-to-risk assessment in subjects receiving ipilimumab. The DMC charter includes explicit stopping rules for some studies, allowing the DMC to recommend discontinuing further treatment across the ipilimumab program if necessary.

1.4.5 Clinical Efficacy of Ipilimumab

MDX010-20, a randomized, controlled, second line clinical trial for patients with locally advanced/metastatic melanoma established the clinical efficacy of single agent ipilimumab at a dose of 3 mg/kg administered every 3 weeks for 4 doses, and led to approval of ipilimumab by the FDA for the treatment of unresectable or metastatic melanoma.

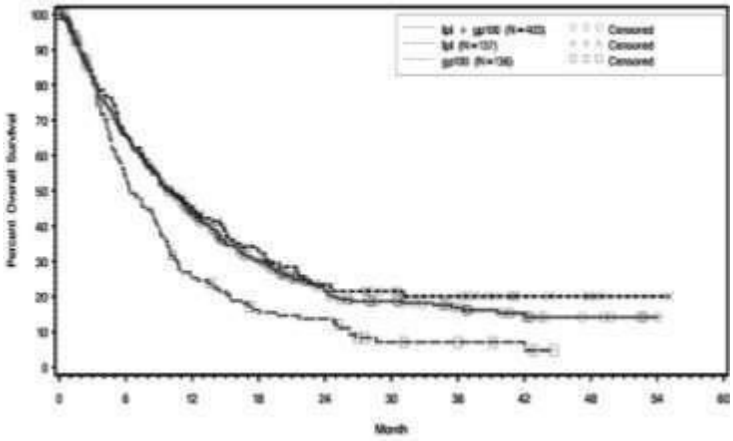
MDX010-20 randomized 676 subjects (3:1:1); 403 were randomized to receive ipilimumab at 3 mg/kg in combination with an investigational peptide vaccine with incomplete Freund's adjuvant (gp100), 137 were randomized to receive ipilimumab at 3 mg/kg, and 136 were randomized to receive gp100 alone. The study enrolled only subjects with HLA A2*0201 genotype; this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. Assessment of tumor response was conducted at Weeks 12 and 24, and every 3 months thereafter. Subjects with evidence of objective tumor response at 12 or 24 weeks had assessment for confirmation of durability of response at 16 or 28 weeks, respectively. The major efficacy outcome measure was overall survival (OS) in the ipilimumab + gp100 arm compared to that in the gp100 arm. Secondary efficacy outcome measures were OS in the ipilimumab + gp100 arm compared to the ipilimumab arm, OS in the ipilimumab arm compared to the gp100 arm, best overall response rate (BORR) at Week 24 between each of the study arms, and duration of response. Sixty-one (61%) percent of subjects randomized to either ipilimumab -containing arm received all 4 planned doses. The median duration of follow-up was 8.9 months. The OS results are shown in Table 4 and Figure 2.

Table 4: MDX010-20 Overall Survival Results

	Ipilimumab n = 137	Ipilimumab + gp100 n = 403	gp100 n = 136
Hazard Ratio (vs gp100) (95% CI)	0.66 (0.51, 0.87)	0.68 (0.55, 0.85)	
p-value	p = 0.0026[a]	p = 0.0004	
Hazard Ratio (vs ipilimumab) (95% CI)		1.04 (0.83, 1.30)	
Median (months) (95% CI)	10 (8.0, 13.8)	10 (8.5, 11.5)	6 (5.5, 8.7)

a Not adjusted for multiple comparisons

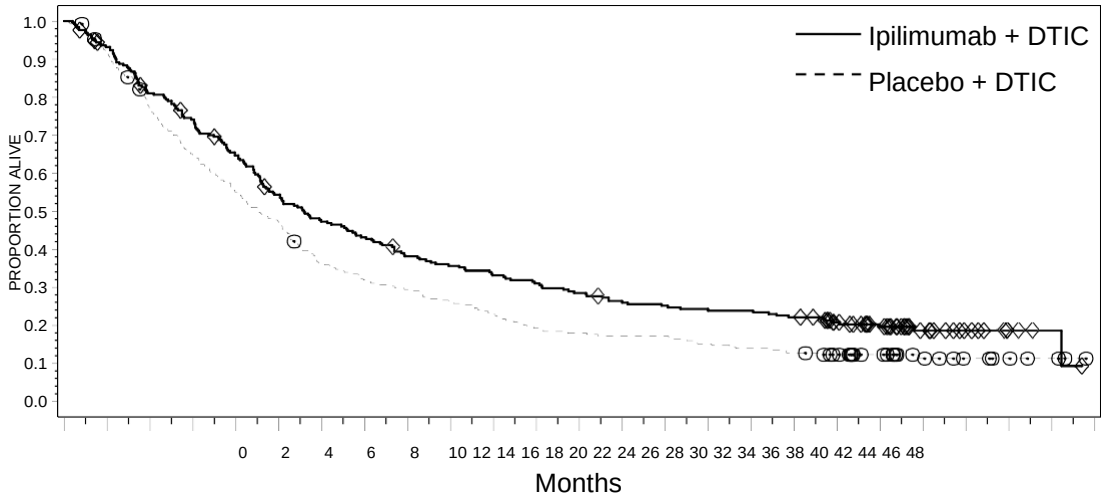
Figure 2: MDX010-20 - Overall Survival by Treatment (ITT Population)



The best overall response rate (BORR) as assessed by the investigator was 5.7% (95% CI: 3.7%, 8.4%) in the ipilimumab + gp100 arm, 10.9% (95% CI: 6.3%, 17.4%) in the ipilimumab arm, and 1.5% (95% CI: 0.2%, 5.2%) in the gp100 arm. The median duration of response was 11.5 months in the ipilimumab + gp100 arm and has not been reached in the ipilimumab or gp100 arm.

Patients on the ipilimumab arm received a median of 3 ipilimumab induction doses. A total of 17.4% and 21.1% of patients continued to receive maintenance ipilimumab or placebo, for a median of 4 and 2 doses, respectively. The number of patients who received all 8 dacarbazine doses was 12.2% in the ipilimumab arm, and 21.5% in the placebo arm. The study met its primary end-point of prolonging overall survival in patients treated with ipilimumab (HR 0.72 (95% CI, 0.59 – 0.87), median OS 11.2 vs 9.1 months, p = 0.0009). The OS Kaplan-Meier curve is presented in Figure 3.

Figure 3: CA184024 Kaplan-Meier Plot of Overall Survival - All Randomized Subjects



Three year survival rates were 20.8% in the ipilimumab arm, and 12.2% in the placebo arm. BORR was increased from 10.3% in the placebo arm to 15.2% in the ipilimumab arm (Table 5). More importantly, duration of response was more than twice as long in the ipilimumab arm (19.3 months) than in the placebo arm (8.1 months).

Table 5: CA184024 Tumor Response

	Ipilimumab + DTIC n = 250	**Placebo + DTIC n = 252**
Disease Control Rate, n (%)	83 (33.2)	76 (30.2)
BORR (CR + PR), n (%)	38 (15.2)	26 (10.3)
Complete response	4 (1.6)	2 (0.8)
Partial response	34 (13.6)	24 (9.5)
Stable disease	45 (18.0)	50 (19.8)
Progressive disease	111 (44.4)	131 (52.0)
Duration of response, months	19.3	8.1

1.4.6 Efficacy of Ipilimumab in Other Malignancies

Ipilimumab is being evaluated in 7 Phase 1 and 2 studies in prostate cancer, 4 of which are completed (MDXCTLA4-01, MDX010-07, MDX010-17, and MDX010-21,) and 3 of which are ongoing. Final efficacy results from the 4 completed studies and preliminary efficacy results from 2 of the 3 ongoing studies are presented in Table 5. In these studies, ipilimumab was administered at a range of doses (0.3 to 10 mg/kg) alone or in combination with docetaxel, prostate cancer vaccine, or radiation directed at bone lesions. Although sample sizes were small, response as measured by ≥ 50% decline in prostate-specific antigen (PSA) was reported across 3- to 10-mg/kg doses (Table 5). Responses were durable, ranging between approximately 2 and 24 months. Studies in lung cancer, and renal cell cancer are currently ongoing.

1.4.7 Ipilimumab: Clinical Data in Lymphoma

In non-Hodgkin lymphoma (NHL) ipilimumab was investigated in a Phase 1 single agent study by Ansell et al (58). Treatment consisted of ipilimumab at 3mg/kg for an initial dose, and then monthly at 2 dose levels, first 1mg/kg and then 3mg/kg. 18 patients were treated: 12 at the lower dose, and 6 at the higher dose level. Ipilimumab was generally well tolerated with the most common adverse events including diarrhea, headache, abdominal pain, anorexia, fatigue, neutropenia and thrombocytopenia. Five patients had grade 3 diarrhea, and a single patient had grade 3 fatigue; otherwise all toxicities were grades 1 and 2. No grade 4 toxicities were described. Neurotoxicity and pulmonary toxicity were not described. Two patients demonstrated clinical response; 1 patient with DLBCL has had an ongoing CR for + 31 months, a second with FL had a partial response lasting 19 months. In 5/16 patients (31%) T cell proliferation to recall antigen was significantly increased (> 2 fold) after ipilimumab therapy. There is to date no study which investigates ipilimumab exclusively in the HL population. HL patients were included however, in an intriguing study of patients with relapsed malignancy after alloSCT. Patients received ipilimumab at doses between 0.1 and 3.0 mg/kg. Dose limiting toxicity and GVHD were not seen. Three patients with lymphoma developed objective responses; 2 CRs in patients with HL were seen at the 3.0mg/kg dose level, and one PR was seen in a patient with refractory MCL. Both HL patients had relapsed within 100 days of transplantation, and failed to respond to subsequent donor lymphocyte infusion (DLI) prior to treatment with ipilimumab. Duration of response for the 2 HL patients was 37+ months, and 9 months. (59). No study to date in HL or NHL has investigated ipilimumab in combination with a tumor targeting therapy. In melanoma when ipilimumab was combined with cytotoxic chemotherapy (dacarbazine) overall survival (OS) was superior in the group receiving the combined immuno-chemotherapy to patients receiving the cytotoxic chemotherapy dacarbizine as a single agent (60).

1.4.8 Association of Immune Adverse Events with Improved Overall Survival

Results from MDX010-20 suggested a tendency for improved OS in subjects with any irAEs; the presence or absence of Grade 3-5 irAEs did not appear to influence OS. In CA184024, analyses using the Cox proportional hazards model were conducted to assess the association of irAEs and OS. Overall, the results show a significant improvement in OS in subjects with any Grade 3/4 irAEs and liver Grade 3/4 AEs. These results should be interpreted withcaution, as the analysis was not adjusted for other prognostic factors

1.4.9 Overall Risk/Benefit Assessment of Ipilimumab Studies

Ipilimumab is the first drug to demonstrate prolonged survival in subjects with pre-treated advanced melanoma, based on a large, multinational, double-blind, pivotal, Phase 3 study supported by a

comprehensive Phase 2 program. The unique immune-based mechanism of action is reflected in the clinical patterns of anti-cancer activity in some patients. Ipilimumab impacts tumor cells indirectly, and measurable clinical effects emerge after the immunological effects. Tumor infiltration with lymphocytes and the associated inflammation (documented by biopsy in some subjects) is likely the cornerstone of the effect of ipilimumab and can manifest in various patterns of clinical activity leading to tumor control. In some cases, inflammation may not be noted by radiological examination and objective response is observed with the first tumor assessment in a manner seen in patients receiving other types of anti-cancer treatments. In other cases, response may be preceded by an apparent increase in initial tumor volume and/or the appearance of new lesions, which may be mistaken for tumor progression on radiological evaluations. Therefore, in subjects who are not experiencing rapid clinical deterioration, confirmation of progression is recommended, at the investigator's discretion, to better understand the prognosis as well as to avoid unnecessarily initiating potentially toxic alternative therapies in subjects who might be benefitting from treatment. Immune-related (ir) response criteria were developed based on these observations to systematically categorize novel patterns of clinical activity and are currently being prospectively evaluated in clinical studies.

In metastatic diseases, stabilization is more common than response, and in some instances is associated with slow, steady decline in tumor burden over many months, sometimes improving to partial and/or complete responses. Thus, the immune-based mechanism of action of ipilimumab results in durable disease control, sometimes with novel patterns of response, which contribute to its improvement in OS. The immune-based mechanism of action is also reflected in the safety profile. The most common drug-related AEs are immune-mediated, consistent with the mechanism of action of the drug and generally medically manageable with topical and/or systemic immunosuppressants. As previously discussed, the immune-mediated adverse reactions primarily involve the GI tract, skin, liver, endocrine glands, and nervous system.

The early diagnosis of immune-mediated adverse reactions is important to initiate therapy and minimize complications. Immune-mediated adverse reactions are generally manageable using symptomatic or immunosuppressive therapy as recommended through detailed diagnosis and management guidelines, as described fully in the current IB. The management guidelines for general immune-mediated adverse reactions and ipilimumab-related GI toxicities, hepatotoxicity, endocrinopathy, and neuropathy are provided in the appendices of the current IB.

In summary, ipilimumab offers clinically meaningful and statistically significant survival benefit to patients with pre-treated advanced melanoma and evidence of clinical activity in randomized studies in other tumor types. These findings, together with evidence of a safety

profile that is manageable with careful monitoring and appropriate intervention for treatment of immune-mediated toxicities, suggest an acceptable benefit to risk ratio.

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As of July 12, 2016, accrual to arms A, B, and C, have been completed and the MTD for ipilimumab in the brentuximab vedotin/ipilimumab combination was determined to be 3 mg/kg.

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1.4.10 Nivolumab

Nivolumab (BMS-936558, MDX-1106, and ONO-4538) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that is specific for human programmed death-1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor (Investigator Brochure, 2014 78). PD-1 is a negative regulatory molecule that is expressed transiently following T-cell activation and on chronically stimulated T cells characterized by an “exhausted” phenotype. Nivolumab binds to cynomolgus monkey PD-1 but not mouse, rat, or rabbit molecules. Clinical activity of nivolumab has been observed in patients with melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). The combination of nivolumab and ipilimumab (anti-cytotoxic T lymphocyte associated antigen-4 [anti-CTLA-4]) in a phase 1/2 trial showed markedly enhanced clinical activity with an acceptable safety profile in melanoma patients (Wolchok et al., 201389).

The clinical use of monoclonal antibodies to T-cell inhibitory receptors has provided transformative information on the nature of the immune system and cancer. An emerging picture suggests that endogenous immune responses can mediate effective tumor regression and/or improved survival even in patients with large volume tumors resistant to other forms of therapy. Some of the unique features of this type of therapy, based largely on experience in advanced melanoma, include: improved overall survival (OS) with or without radiographic responses or improved progression-free survival (PFS); responses that may be delayed or occur after radiographic disease progression; combinations of immune modulators with enhanced or novel activities (in the example of ipilimumab and nivolumab); and toxicity that is almost exclusively immune or inflammatory in nature. It is not yet clear what factors determine responses and which components of the immune system are needed for this to occur. It seems likely that both memory helper and effector cells would be needed to sustain long-term responses. Increasing emphasis has been placed on understanding the relationships of the tumor, cellular infiltrate, and immunologic milieu surrounding each tumor.

PD-1, a 55-kDa type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include Ig super family member CD28, CTLA-4, inducible co-stimulator (ICOS), and B and T lymphocyte attenuator (BTLA) (Investigator Brochure, 201478). PD-1 is transiently but highly expressed on activated T cells functioning to limit immune effectors at the site of activation. Chronic stimulation may prevent the re-methylation of the PD-1 gene leading

to continuous expression and characterizes a state of “exhausted” T cells that lose function and proliferative capacity while enhancing a suppressive tumor microenvironment. PD-1 may act together with other T-cell modulating molecules, including CTLA-4, TIM-3, lymphocyte-activation gene 3 (LAG-3) as well as indoleamine-pyrrole 2,3-dioxygenase 1 (IDO-1), cytokines, and transforming growth factor beta (TGF-beta).

Two ligands specific for PD-1 have been identified: PD-ligand 1 (PD-L1, also known as B7-H1 or CD274, expressed on tumor, antigen-presenting cells [APCs], and dendritic cells [DCs]) and PD-L2 (also known as B7-DC or CD273, expressed on endothelial cells). The interaction of PD-1 with PD-L1 and PD-L2 results in negative regulatory stimuli that down-modulate the activated T-cell immune response through SHP-1 phosphastase.

PD-1 knockout mice develop strain-specific lupus-like glomerulonephritis (C57BL/6) and cardiomyopathy (BALB/c). In transplantable tumor models that expressed PD-1 and LAG-3 on tumor-infiltrating CD4+ and CD8+ T cells dual anti-LAG-3/anti-PD-1 antibody treatment cured most mice of established tumors that were largely resistant to single antibody treatment (Woo et al., 201290). Despite minimal immunopathologic sequelae in PD-1 and LAG-3 single knockout mice, dual knockout mice abrogated self-tolerance with resultant autoimmune infiltrates in multiple organs, leading to eventual lethality.

PD-L1 expression is found on a number of tumors, and is associated with poor prognoses based on OS in many tumors, including melanoma (Taube et al., 201284), renal (Thompson et al., 2004; Thompson et al., 2005; Thompson et al., 200685, 86, 87), esophageal (Ohigashi, et al. 200581), gastric (Wu et al., 200691), ovarian (Dong et al., 200374), pancreatic (Nomi, et al., 200780), lung (Zitvogel, et al., 200692), and other cancers (Investigator Brochure, 201478).

The PD-1/PD-L1 axis plays a role in human infections, particularly in hepatitis C virus (HCV) and human immunodeficiency virus (HIV). In these cases, high expression levels of PD-1 were found in viral-specific CD8+ T cells that also display a non-responsive or exhausted phenotype. Non-responsive PD-1-high T cells were observed in simian immunodeficiency virus (SIV) infection in rhesus macaques. Treatment of SIV-infected macaques with an anti-PD-1 mAb (3 mg/kg x4) resulted in decreased viral loads and increased survival along with expanded T cells with increased T-cell functionality.

1.4.10.1 Nonclinical Development of Nivolumab

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab alone was well tolerated (Investigator Brochure, 201478). Combination studies have highlighted the potential for toxicity when combined with ipilimumab, MDX-1408, and BMS-986016. Nivolumab bound specifically to PD-1 (and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA)

with a Kd = 3.06 nM. A surrogate rat anti-mouse PD-1 antibody (4H2) was derived and expressed as chimeric IgG1 murine antibody. Antitumor activity was seen for several tumor models, including colon carcinoma and fibrosarcoma.

1.4.10.2 Clinical Development of Nivolumab

Nivolumab is being evaluated as monotherapy and in combination with cytotoxic chemotherapy, other immunotherapy (such as ipilimumab), anti-angiogenesis therapy, and targeted therapies in completed and ongoing BMS-sponsored clinical trials in NSCLC, melanoma, RCC, hepatocellular carcinoma (HCC), gastrointestinal (GI) malignancies including microsatellite instability (MSI) in colorectal cancer, and triple-negative breast cancer (TNBC) with an expanding group of indications (Investigator Brochure, 201478). In addition, two investigator-sponsored trials (ISTs) of nivolumab in combination with a peptide vaccine in melanoma are being conducted in the adjuvant setting and advanced disease.

Seven nivolumab studies were conducted in Japan, including six studies in advanced solid tumors and recurrent or unresectable stage III/IV melanoma sponsored by Ono Pharmaceuticals Co. Ltd., and one IST in recurrent or advanced platinum-refractory ovarian cancer.

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1.4.10.3 Pharmacokinetics

Pharmacokinetics (PK) of nivolumab was linear in the range of 0.3 to 10 mg/kg, with dose-proportional increases in maximum serum concentration (Cmax) and area under the concentration-time curve from time zero to infinity (AUC0-∞), with low to moderate inter-subject variability observed at each dose level (Investigator Brochure, 201478). Clearance of nivolumab is independent of dose in the dose range (0.1 to 10 mg/kg) and tumor types studied. Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights. The mean terminal elimination half-life of BMS-936558 is 17 to 25 days consistent with the half-life of endogenous IgG4.

Support for Dosing Rationale

The nivolumab dose of 360 mg Q3W was selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, non-small-cell lung cancer [NSCLC], and renal cell carcinoma [RCC]) where body weight normalized dosing (mg/kg) has been used.

Population PK analyses have shown that the exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks, and no clinically meaningful differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as the body weight increases, but less than proportionally with increasing weight, indicating that mg/kg dosing represents an over-adjustment for the effect of body weight on nivolumab PK. Using the PPK model, the overall distributions of nivolumab average steady-state exposures (Cavgss) are comparable after treatment with either nivolumab 3 mg/kg Q2W or 360 mg Q3W. The flat dose regimen of 360 mg Q3W is predicted to result in approximately 23% higher maximum steady state concentrations (Cmaxss) and approximately 6% lower steady state trough concentrations (Cminss) compared to the reference regimen of 3 mg/kg Q2W. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Although nivolumab Cmaxss is predicted to be higher following 360 mg Q3W, these exposures are predicted to be within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program, and are not considered to put participants at increased risk. The exposures predicted following administration of nivolumab 360 mg Q3W are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC, and are not predicted to affect efficacy. Based on these data, nivolumab 360 mg Q3W is expected to have similar efficacy and safety profiles to nivolumab 3 mg/kg Q2W.

Pharmacokinetics Supporting Dosing Rationale

The pharmacokinetics (PK) of nivolumab was studied in subjects over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Based on a population pharmacokinetic (PPK) analysis using data from patients with various tumor types, including melanoma, NSCLC, and RCC and a time varying CL model, nivolumab clearance was shown to decrease over time, with a median maximal reduction from baseline values of approximately 25% resulting in a geometric mean steady state clearance (CLss) (% coefficient of variation [CV%]) of 8.2 mL/h [53.9%]. The decrease in CLss is not considered to be clinically relevant. The geometric mean [CV%] volume of distribution at steady state (Vss) is 6.8 L (27.3%), and

elimination half-life (t1/2) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by approximately 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1, solid tumor type, baseline tumor size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin, and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. PPK analysis suggested that nivolumab CL in subjects with cHL was approximately 32% lower relative to subjects with NSCLC; however, the lower CL in cHL subjects was not considered to be clinically relevant as nivolumab exposure was not a significant predictor for safety risks for these patients.

1.4.10.4 Efficacy

In a phase 1 (1, 3, and 10 mg/kg nivolumab doses) dose-escalation study the 3 mg/kg dose was chosen for expanded cohorts. Among 236 patients, objective responses (ORs) (complete or partial responses [CR or PR]) were seen in NSCLC, melanoma, and RCC. ORs were observed at all doses (Sznol et al., 201383). Median OS was 16.8 months across doses and 20.3 months at the 3 mg/kg dose. Median OS across all dose cohorts was 9.2 months and 9.6 months for squamous and non-squamous NSCLC, respectively (Brahmer et al., 201373). In the RCC cohort, median duration of response was 12.9 months for both doses with 5 of the 10 responses lasting ≥1 year (Drake et al., 201376).

In an advanced melanoma phase 1 study, nivolumab and ipilimumab were administered IV every 3 weeks for 4 doses followed by nivolumab alone every 3 weeks for 4 doses (concurrent regimen) (Wolchok et al., 201389). The combined treatment was subsequently administered every 12 weeks for up to 8 doses. In a sequenced regimen, patients previously treated with ipilimumab received nivolumab every 2 weeks for up to 48 doses. In the concurrent regimen (53 patients), 53% of patients had an OR at doses 1 mg/kg nivolumab and 3 mg/kg ipilimumab, with tumor reduction of 80% or more (modified World Health Organization [mWHO] criteria). In the sequenced-regimen (33 patients), the objective response rate (ORR) was 20%.

In a phase 1 study of nivolumab plus platinum-based doublet chemotherapy (PT-doublet) in chemotherapy-naïve NSCLC patients, 43 patients were treated with nivolumab + PT-doublet (Rizvi et al., 201382). No dose-limiting toxicities (DLTs) were reported and total/confirmed ORRs were 43/33%, 40/33%, and 31/31% in nivolumab/gemcitabine/cisplatin, nivolumab/pemetrexed/cisplatin, and nivolumab/carboplatin/paclitaxel arms, respectively.

In a recently described phase 1 study of nivolumab as a single agent in patients with relapsed Hodgkin lymphoma, 23 patients were treated with Nivolumab 3mg/kg every two weeks until they had a complete response, tumor progression, or excessive toxic effects. The ORR was 87% including 17% with complete response and 70% with partial response. The rate of progression free survival at 24 weeks was 86%.

1.4.10.5 Toxicology

A maximum tolerated dose (MTD) of nivolumab was not defined (Topalian et al., 201288). Serious adverse events (SAEs) occurred in 32 of 296 patients (11%) similar to the immune-related inflammatory events seen with ipilimumab: pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis (with noted pulmonary toxicity resulting in 3 deaths. Renal failure, symptomatic pancreatic and DM, neurologic events, and vasculitis have also been reported.). In combination with ipilimumab in the concurrent-regimen group (Wolchok et al., 201389), grade 3 or 4 treatment-related events were noted in 53% of patients. Skin rash represents the majority of these events.

1.4.10.6 Pharmacodynamics/Biomarkers

Tumor-cell expression (melanoma) of PD-L1 was characterized in combination with ipilimumab with the use of IHC staining and pharmacodynamics changes in the peripheral-blood absolute lymphocyte count (Wolchok et al., 201389). With PD-L1 positivity defined as expression in at least 5% of tumor cells, biopsy specimens from 21 of 56 patients (38%) were PD-L1–positive. Among patients treated with the concurrent regimen of nivolumab and ipilimumab, ORs were observed in patients with either PD-L1–positive tumor samples (6 of 13 patients) or PD-L1–negative tumor samples (9 of 22). In the sequenced regimen cohorts, a higher number of overall responses was seen among patients with PD-L1–positive tumor samples (4 of 8 patients) than among patients with PD-L1–negative tumor samples (1 of 13) suggesting the possibility that these tumors have higher response rates to the

combination. The relationship between PDL-1 expression and responses may not be present in patients treated with the combination. Tissue expression of PDL-2, interferon-γ (IFN- γ), IDO, and T cell CD8+ are of current interest. Until more reliable data based on standardized procedures for tissue collection and assays are available, PD-L1 status cannot be used to select patients for treatment at this time.

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1.4.10.7 Rationale for Nivolumab 30-minute Infusion

Long infusion times place a burden on participants and treatment centers. Establishing that nivolumab can be safely administered using shorter infusion times of 30-minutes duration in participants will diminish the burden, provided no change in safety profile. Previous clinical studies show that nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over long treatment duration. In Study CA209010, (a Phase 2, randomized, double blinded, dose-ranging study of nivolumab in participants with advanced/metastatic clear cell RCC) a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg, and 18.5% at 10 mg/kg). All the events were Grade 1 - 2 and were manageable. An infusion duration of 30 minutes for 360 mg doses of nivolumab is not expected to present safety concerns compared to the prior experience at 10-mg/kg nivolumab dose infused over a 60-minute duration.

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1.4.11 Ipilimumab and Nivolumab

Ipilimumab (BMS-734016, MDX010, MDX-CTLA4, YervoyTM) is a fully human monoclonal immunoglobulin (Ig) G1κ specific for human cytotoxic T lymphocyte antigen 4 (CTLA-4, CD152), which is expressed on a subset of activated T cells (Ipilimumab Investigator Brochure, 201479). CTLA-4 is a negative regulator of T-cell activation. Ipilimumab binds to CTLA-4 and inhibits its interaction with ligands on antigen-presenting cells (APCs). The proposed mechanism of action for ipilimumab's effects in subjects with melanoma is indirect, possibly through T-cell potentiation and mediation of antitumor immune responses.

Ipilimumab has been approved for the treatment of unresectable metastatic melanoma in over 40 countries including the United States (US, March 2011), the European Union (July 2011), and Australia (July 2011).

BMS and Medarex (acquired by BMS in Sep-2009) have co-sponsored an extensive clinical development program for ipilimumab, encompassing > 13,800 subjects in several cancer types in completed and ongoing studies, including a compassionate use program (Ipilimumab Investigator Brochure, 201479). The focus of the clinical program is in melanoma, prostate cancer, and lung cancer, with advanced melanoma being the most comprehensively studied

indication. Ipilimumab is being investigated both as monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies.

CTEP's clinical development of ipilimumab focuses on cervical, gastrointestinal, ovarian, prostate cancer, chronic lymphocytic leukemia, head and neck squamous cell carcinoma, solid tumors, Hodgkin and non-Hodgkin lymphomas, melanoma, and myelodysplastic syndrome.

While the toxicity and clinical responses overlap, mechanisms of immune activation and range of responses appear to be different for each of the single agents.

Preclinical data support the combinations of nivolumab and ipilimumab (Curran et al., 201075).

The combination of ipilimumab with nivolumab has been reported to result in improved responses in advanced melanoma marked by time to response, number of responses, depth and duration of responses, PFS, and OS compared to single agent ipilimumab (Wolchok et al., 201389).

For RCC results have been reported (Hammers et al., 201477).

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The combination is being evaluated in other disease settings typically with 3mg/kg nivolumab and 1mg/kg ipilimumab. Given the available safety data for this treatment combination, this dosing schedule was chosen to take forward into the triplet combination of nivolumab, ipilimumab, and brentuximab vedotin.

See Sections 8.1 and 8.3 or the Investigator's Brochures for drug information.

1.5 The Rationale for Synchronously Targeting Malignant and Reactive Cells

The above described studies suggest that targeting immunomodulatory T cells, even in the absence of cytotoxic chemotherapy has striking activity in a small number of hodgkin and non-hodgkin lymphoma patients. Blockade of CTLA-4 with ipilimumab and nivolumab will increase the population of activated T effector cells in the HL microenvironment, which can target and kill HRS tumor cells. However, to maximize the CR rate, clearly strategies are needed which combine this immunomodulatory approach with tumor targeting agents which can both deplete tumor cell bulk, and release antigen to further stimulate an immune effector response. The ideal tumor targeting platform is one which targets the tumor cells specifically and alters the balance of the tumor microenvironment from tumor tolerant to tumor directed cytotoxicity.

1.6 Brentuximab Vedotin: A Rational Targeted Strategy in Hodgkin Lymphoma

1.6.1 Background and Mechanism for Brentuximab Vedotin

Brentuximab vedotin is an antibody drug conjugate (ADC) directed against the CD30 antigen, which was developed to treat patients with CD30-positive hematologic malignancies. The cell surface antigen CD30 is a member of the tumor necrosis receptor super-family. CD30

is expressed primarily on the HRS cells of HL and in anaplastic large cell lymphoma (ALCL), however CD30 expression has also been reported in: Kaposi's sarcoma (KS), cutaneous T-cell lymphomas (CTCL), a fraction of diffuse large B-cell lymphomas (DLBCL), some follicular lymphomas, and other lymphoproliferative diseases (14-17). CD30 in normal lymphocytes is expressed only by activated B cells and T cells, and for the latter CD30 is preferentially expressed by activated T cells producing T helper 2 (Th2) type B cell stimulatory cytokines.

The structure of brentuximab vedotin is composed of the chimeric antibody cAC10 (SGN-30) modified by the addition of a valine–citrulline peptide linker to monomethyl auristatin E (MMAE), a synthetic analogue of the naturally occurring anti-mitotic agent dolastatin 10. Brentuximab vedotin has a multistep mechanism of action that is initiated by binding to CD30 on the cell surface, followed by clathrin-mediated endocytosis. MMAE is released in the lysosome from its conjugate through proteolytic degradation of the peptide linker (61). The binding of released MMAE to tubulin disrupts the microtubule network, leading to G2/M phase cell cycle arrest and apoptosis (62). Overall efficacy of the ADC may be enhanced by the fact that a small fraction of drug diffuses out of the targeted tumor cell, and exerts cytotoxic effects on the surrounding tumor microenvironment, but brentuximab vedotin is unique in that it targets via CD 30 the HL HRS cells selectively, and largely spares the surrounding tumor microenvironment.

1.6.2 Preclinical Data for Brentuximab Vedotin

Preclinical and toxicologic studies of brentuximab vedotin demonstrated antitumor activity in both *in vitro* and *in vivo* models. The toxicity of multiple doses of brentuximab vedotin has been assessed in rats and monkeys. In both species, hypocellularity of the bone marrow and lymphoid depletion of the thymus were observed. Histopathologic lesions were also observed in the spleen in monkeys and in the liver and testes in rats. In addition, decreases in peripheral blood counts were observed in both species, and elevations in liver enzymes were seen in rats only. The most significant clinical toxicity was neutropenia, observed in monkeys, which resulted in secondary bacterial infections leading to early deaths at the 6 mg/kg dose. Toxicity was dose-dependent, with a no-observable-adverse-effect level of 0.5 mg/kg in rats and 1 mg/kg in monkeys (Investigator's Brochure).

1.6.3 Clinical Safety of Brentuximab Vedotin

In phase 1, a single-arm, open-label, dose-escalation study of brentuximab vedotin was been conducted in patients with CD30-positive hematologic malignancies. In this study, 42 evaluable patients received brentuximab vedotin at doses ranging from of 0.1 to 3.6 mg per kilogram of body weight on Day 1 of a 21-day cycle. Tumor response assessments were performed between the second and third cycle of therapy. Brentuximab vedotin was generally well-tolerated at

doses of up to 1.8 mg/kg. The most common adverse events reported were: fatigue (16 patients, 36%), pyrexia (15 patients, 33%), and diarrhea, nausea, neutropenia, and peripheral neuropathy (10 patients, 22% each). At the 1.2 mg/kg dose level (one level below the MTD) there were no grade 3 or 4 adverse events. Grade 3 neutropenia, back pain, and limb pain each occurred in 1 patient out of 12 (25%) at the 1.8 mg/kg dose level. There were no grade 4 adverse events at the 1.8mg/kg dose level. At the higher dose levels grade 3 neutropenia and pyrexia was seen in 2 of 12 (17%) of patients who received the 2.7mg/kg dose, and grade 4 neutropenia and pyrexia in 1 of 1 (100%) of patients receiving the 3.6 mg/kg dose (63).

Two phase 2 studies (SG035-0003 and SG035-0004) evaluating the efficacy and safety of brentuximab vedotin as a single agent were performed in patients with relapsed or refractory Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (ALCL). Overall, 20% of HL patients and 28% of systemic ALCL patients in phase 2 studies discontinued treatment because of AEs. Treatment-emergent adverse events (AEs) occurring in ≥ 20% of HL and systemic ALCL patients in the phase 2 studies were peripheral sensory neuropathy (45%), fatigue (43%), nausea (41%), diarrhea (34%), pyrexia (31%), upper respiratory tract infection (31%), neutropenia (21%), and vomiting (20%). These events were primarily Grade 1 or 2, with the exception of neutropenia, for which Grade 3 and Grade 4 events were reported for 13% and 7% of patients, respectively. Similar patterns and incidences of AEs were generally observed for HL and ALCL patients (4) .

Additional clinical studies, compassionate use programs, and postmarketing use have contributed further brentuximab vedotin safety data. Notable adverse events observed to date include peripheral neuropathy, infusion-related reactions, and neutropenia; and, less commonly, progressive multifocal leukoencephalopathy (PML), Stevens-Johnson syndrome (SJS), and tumor lysis syndrome (TLS). In addition, concomitant use of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity that occurred in some patients receiving concomitant brentuximab vedotin and bleomycin; two events of pulmonary toxicity led to death (64).

AEs that occurred in ≥ 10% of either HL or systemic ALCL patients in completed phase 2 studies are summarized in Table 7.

Table 7 Treatment-emergent adverse events occurring in ≥ 10% of HL or systemic ALCL patients in completed phase 2 studies (Studies SG035-0003 and SG035-0004)

	HL SG035-0003 (N=102) % patients			ALCL SG035-0004 (N=58) % patients		
Preferred Term	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Peripheral sensory neuropathy	48 (47)	8 (8)	0	24 (41)	7 (12)	0
Fatigue	47 (46)	2 (2)	0	22 (38)	2 (3)	1 (2)
Nausea	43 (42)	0	0	23 (40)	1 (2)	0
Diarrhoea	37 (36)	1 (1)	0	17 (29)	2 (3)	0
Pyrexia	30 (29)	2 (2)	0	20 (34)	1 (2)	0
Upper respiratory tract	38 (37)	0	0	11 (19)	0	0
Neutropenia	22 (22)	14 (14)	6 (6)	12 (21)	7 (12)	5 (9)
Vomiting	22 (22)	0	0	10 (17)	2 (3)	0
Cough	21 (21)	0	0	10 (17)	0	0
Headache	19 (19)	0	0	11 (19)	1 (2)	0
Constipation	16 (16)	0	0	13 (22)	1 (2)	0
Rash	14 (14)	0	0	14 (24)	0	0
Pruritus	16 (16)	0	0	11 (19)	0	0
Myalgia	17 (17)	0	0	9 (16)	1 (2)	0
Arthralgia	19 (19)	0	0	5 (9)	0	0
Dyspnoea	13 (13)	1 (1)	0	11 (19)	1 (2)	0
Insomnia	14 (14)	0	0	9 (16)	0	0
Abdominal pain	17 (17)	1 (1)	1 (1)	5 (9)	1 (2)	0
Alopecia	13 (13)	0	0	8 (14)	0	0
Chills	13 (13)	0	0	8 (14)	0	0
Decreased appetite	11 (11)	0	0	9 (16)	1 (2)	0
Dizziness	11 (11)	0	0	9 (16)	0	0
Back pain	14 (14)	0	0	5 (9)	1 (2)	0
Pain in extremity	10 (10)	0	0	8 (14)	1 (2)	1 (2)
Lymphadenopathy	11 (11)	0	0	6 (10)	0	0
Muscle spasms	9 (9)	0	0	8 (14)	1 (2)	0
Night sweats	12 (12)	0	0	4 (7)	0	0
Thrombocytopenia	8 (8)	6 (6)	2 (2)	8 (14)	5 (9)	3 (5)
Anaemia	9 (9)	5 (5)	1 (1)	6 (10)	4 (7)	0
Anxiety	11 (11)	2 (2)	0	4 (7)	0	0
Oropharyngeal pain	11 (11)	0	0	4 (7)	0	0
Peripheral motor neuropathy	12 (12)	1 (1)	0	3 (5)	2 (3)	0
Weight decreased	6 (6)	0	0	8 (14)	2 (3)	0
Pain	7 (7)	0	0	6 (10)	0	1 (2)
Oedema peripheral	4 (4)	0	0	8 (14)	0	0
Dry skin	4 (4)	0	0	6 (10)	0	0

1.6.4 Peripheral Neuropathy

The incidence and severity of peripheral neuropathy was evaluated for patients in SG035-0003 and SG035-0004 using the PN SMQ (MedDRA version 13.0), which includes terms for both sensory and motor neuropathy, and graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 3.0). In the two completed phase 2 studies 89 patients (56%) had at least 1 treatment-emergent AE within the PN SMQ. The peripheral neuropathy symptoms that occurred in ≥5% of HL or ALCL patients were peripheral sensory neuropathy (47% HL, 41% ALCL), peripheral motor neuropathy (12% HL, 5% ALCL), paraesthesia (9% ALCL), and neuralgia (5% ALCL). Peripheral neuropathy was primarily Grades 1 and 2 in severity, however 11 HL patients and 10 ALCL patients had Grade 3 peripheral neuropathy. No Grade 4 events were observed. The onset of neuropathy appeared to be correlated with cumulative exposure to drug, with a median time to onset of any grade event of approximately 12.4 (HL) to 15.0 (ALCL) weeks, and to worsen with longer treatment exposure. Median time to onset of Grade 2 neuropathy was 27.3 weeks for HL patients and 17.0 weeks for ALCL patients. Median time to onset of Grade 3 neuropathy was 38.0 weeks for HL patients and 36.1 weeks for ALCL patients. Dose reduction and dose delay, allowed patients with neuropathy to continue treatment. The majority of patients who developed peripheral neuropathy had resolution or improvement of some events at last follow-up. At last follow-up, the majority of patients with ongoing peripheral neuropathy had Grade 1 or 2 symptoms and the majority of patients with Grade 3 neuropathy had experienced improvement or resolution.

1.6.5 Clinical Efficacy of Brentuximab Vedotin

In Phase 1, two studies evaluated the antitumor effect of brentuximab vedotin: in SG035-0001 brentuximab vedotin was given IV, every 3 weeks, and in SG035-0002 brentuximab vedotin was given IV, weekly for the first 3 weeks of every 4-week cycle. In SG035-001 (q 3 weekly dosing) 45 patients were enrolled. Patient enrollment by cohort was as follows: 0.1 mg/kg, 3 patients; 0.2 mg/kg, 4 patients; 0.4 mg/kg, 3 patients; 0.6 mg/kg, 3 patients; 0.8 mg/kg, 3 patients; 1.2 mg/kg, 4 patients; 1.8 mg/kg, 12 patients; 2.7 mg/kg, 12 patients; 3.6 mg/kg, 1 patient. The majority of patients had a diagnosis of HL (42), there were 2 patients with systemic ALCL and 1 patient with angioimmunoblastic T cell lymphoma. All patients had received prior systemic chemotherapy (median, 3 regimens; range, 1-7). In the efficacy evaluable set of 42 patients, objective responses were achieved in 40% (CR for 11 patients (26%), PR for 6 (14%). An additional 17 (40%) had SD, and, 8 (19%) had POD. Objective responses generally occurred at higher doses (≥ 1.2 mg/kg); in patients treated at the maximum tolerated dose (1.8 mg/kg), the objective response rate was 50% (6 of 12 patients). Tumor size reductions were observed in 85% of efficacy evaluable patients.

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Brentuximab vedotin has received accelerated FDA approval based on the Phase 2 pivotal trial in 102 patients with HL relapsed after SCT, which reported an ORR of 73%, a CR of 34%, and a median progression free survival (PFS) of 5.6 months. Notably, 71% of patients had primary refractory disease, defined as not achieving a best response of CR with frontline therapy or relapsing within 3 months of completing front-line therapy. All patients had previously received autologous SCT (1 transplant, 89%; 2 transplants, 11%) and all had received at least one prior regimen of systemic chemotherapy (median 3.5 (range, 1 to 13). In the intent-to-treat (ITT) analysis set of 102 patients, ORR per IRF was 74%, 33% CR (34 patients) and 41% partial remission (PR) (42 patients). The PFS duration was 5.6 months. The remaining patients had SD (22 patients), progressive disease (PD) (3 patients), or were not evaluable for response (1 patient). Tumor size reductions were observed in 94% of all patients (4).

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1.7 Rationale for the Proposed Study

Relapsed and primary refractory HL remains a significant clinical problem, with more than 1,000 primarily young lives lost annually. For these patients tumor targeting therapies alone are inadequate to induce a high complete remission rate, and it is a widely accepted concept that the crosstalk between HRS cell and tumor microenvironment has adapted and evolved under the selection pressure of chemotherapies to generate resistance to standard therapies.

HL is a unique tumor in which a very small number of malignant HRS cells propagate an immunosuppressive peri-tumoral microenvironment with immunomodulatory T cells augmenting HRS growth and survival. The proposed study uses a novel and unique approach of priming the peri-tumoral T cells with ipilimumab and targeting the HRS cells with CD30 specific therapy. This will simultaneously deplete CD30+ bearing HRS cells and create a microenvironment with activated T effector cells that can augment HRS cell killing. We hypothesize that this combinatorial immuno-chemotherapy approach increasing microenvironment activation combined with direct targeting of HRS cells may overcome tumor cell resistance, and will deepen and prolong clinical response in patients with relapsed and refractory HL. Although the tumor microenvironment represents a significant contributor to HL biology, it has not to date been targeted to date by any combination therapy platforms

Histopathologic studies have demonstrated that PD-1 is highly expressed on the peritumoral lymphocytes of the tumor microenvironment of cHL, and correspondingly that the HRS cells themselves express PD-L1[18], suggesting that the PD-1/PD-L1 interaction between the HRS cells and the peritumoral lymphocytes may induce exhaustion in peritumoral lymphocytes contributing to the immune dysfunction and tumor tolerance in the microenvironment. The genes encoding PD-L1/PD-L2 are located on chromosome 9p24.1, which are commonly amplified in nodular sclerosing cHL, the most common histological subtype of cHL, suggesting that this mechanism of immune escape might be of particular relevance in this lymphoma[19]. Epstein barr virus (EBV) infection, which is found in nearly half of cHL patients, may further drive the expression of PD-L1 on the HRS cells[64] in EBV positive patients.

Clinical data with the checkpoint inhibitor nivolumab has recently confirmed the E4412 hypothesis that peritumoral immune activation is a valid therapeutic strategy in HL. Results from the phase 1 trial (CheckMate -039, NCT01592370), were presented at the 56th meeting of the American Society of Hematology (ASH)[65]. Twenty-three patients with relapsed or refractory cHL received 3 mg/kg of nivolumab at week 1, week 4, and then every 2 weeks until disease progression or complete response or for a maximum of 2 years. The primary endpoint was safety; the secondary endpoint was overall response rate (ORR). The ORR for nivolumab was 87% which included 17% CRs; 3 additional patients had stable disease. Evaluation of the median duration of the response in these patients is ongoing; the progression free survival (PFS) rate at 23 weeks was 86%. Analyses of pretreatment tumor specimens from 10 patients revealed copy-number gains in PDL1 and PDL2 and increased expression of these ligands in all 10 patients[66]. This data supported the Breakthrough Therapy Designation for nivolumab, granted in May 2014 by the U.S. Food and Drug Administration (FDA) for the treatment of patients with cHL after failure of ASCT and brentuximab. CheckMate-205 (NCT02181738), a registrational trial evaluating nivolumab in patients with cHL after failure of ASCT, is currently ongoing and recruiting participants.

The strategy of dual checkpoint inhibition with the combination of ipilimumab and nivolumab is safe and highly active in advanced melanoma. In a phase 1 dose-escalation study, combined inhibition of T-cell checkpoint pathways by nivolumab and ipilimumab was associated with a high rate of objective response, including complete responses, among patients with advanced melanoma. In a double-blind study involving 142 patients with metastatic melanoma who had not previously received treatment, patients who received ipilimumab combined with nivolumab or placebo Among patients with BRAF wild-type tumors, the rate of confirmed objective response was 61% (44 of 72 patients) in the group that received both ipilimumab and nivolumab (combination group) versus 11% (4 of 37 patients) in the group that received ipilimumab and placebo (ipilimumab-monotherapy group) ($P < 0.001$), with complete responses reported in 16 patients (22%) in the combination group and no patients in the ipilimumab-monotherapy group. The median duration of response was not reached in either group. The median progression-free survival was not reached with the combination therapy and was 4.4 months with ipilimumab monotherapy (hazard ratio associated with combination therapy as compared with ipilimumab monotherapy for disease progression or death, 0.40; 95% confidence interval, 0.23 to 0.68; $P<0.001$). Similar results for response rate and progression-free survival were observed in 33 patients with BRAF mutation-positive tumors [67].

Despite the striking data for the high activity of both brentuximab vedotin and checkpoint inhibitors in HL, the low CR rate reported with both nivolumab and brentuximab vedotin, confirms that both strategies as single agents, may not be a viable long term strategy for cure, or in maximizing bridge to stem cell transplantation.

The optimal therapeutic strategy to definitively target relapsed/refractory HL must target both components of the lymphoma: depleting the malignant HRS cells which propagate and maintain the dysfunctional tumor microenvironment, and activating the dysfunctional T cells of the tumor microenvironment to enhance their ability to recognize and kill the HRS cells. The antibody drug conjugate

brentuximab vedotin is the ideal agent for HRS tumor targeting as it targets HRS cells directly, and largely spares the microenvironment. Ipilimumab and nivolumab are the ideal agents to combine with brentuximab vedotin, as ipilimumab and nivolumab are tumor microenvironment targeting agents with nivolumab demonstrating clear single agent activity in HL, and demonstrating synergy in solidtumor patients without excessive toxicity.

Thus there is a strong rationale to combine immunomodulatory therapies such a checkpoint inhibitors which have relevance to HL biology and proven activity in HL, with HRS cell-targeting drugs such as brentuximab vedotin. We hypothesize that enhancing the tumor-directed immune activation of the tumor microenvironment, and simultaneously targeting tumor bulk, providing antigen release with a targeted therapy may further stimulate immunity, and develop a platform that may circumvent chemotherapy resistance in relapsed and refractory HL.

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1.8 Summary of Phase I Data

BV + IPI (BI)

E4412 was activated on January 24th, 2014. Since that time, 34 patients have been enrolled. Enrollment was brisk despite limited sites, two mandated study suspensions in 2016 for required amendments due to new risk language of ipilimumab (I) and N, and required study holds between dose escalation cohorts. An abstract reporting the preliminary safety and efficacy of the patients treated on the BI arm was presented as an oral presentation at the American Society of Hematology (ASH) meeting in December. The therapy was well tolerated with few toxicities. For 18 response-evaluable patients who were heavily pretreated, including more than 50% with prior BV the ORR was 72% with a CR rate of 50% and an additional stable disease rate of 17%. This data has been updated for the Cologne Hodgkin meeting and demonstrates for 23 evaluable patients, an overall response (ORR) of 71% with a complete response (CR) rate of 48%. The median progression free survival (PFS) is 1.02 years with a median follow-up of 0.48 years; the median overall survival (OS) has not been reached with a median follow-up of 1.16 years.

BV + NIVO (BN)

In arms D, E, and F of E4412 patients with confirmed R/R HL were treated with N 3mg/kg and BV 1.2mg/kg (Arm D: Dose Level 1) or 1.8mg/kg (Arm E: Dose Level 2) in dose escalation with a 3+3 design and an expansion cohort (Arm F) of 9 patients. BN is given every 21 days for 16 cycles; N may be continued for an additional year (total 2 years of N therapy). As of 3/10/17 19 patients (1 ineligible) have been treated with BN: 3 patients: Arm D, 7 patients: Arm E, 9 patients Arm F. Patients were heavily pretreated with a median of 3 prior therapies. Six patients had prior SCT (5 autologous, 1 allogeneic); 2 patients had prior treatment with BV. Nineteen of 19 patients are evaluable for safety. There were 2 significant treatment related adverse events (AEs): 1 patient in Arm E experienced a DLT (pneumonitis grade 3 with grade 3 dyspnea and hypoxia, and typhilits), and made a full recovery; 1 elderly patient in Arm F had grade 5 pneumonitis occurring in cycle 2. There were no other Grade 4 or 5 AEs; grade 3 AEs were one each: rash, puritis, and neutropenia.

Response Data: Eighteen of 18 eligible patients are evaluable for response. The overall response rate (ORR) for the combination was 89%, with a CR rate of 50% (9/18) (95% CI: 26%-74%). There were 2 CRs and 1 PR in patients treated with prior BV. The 6 month PFS is 91% (95% CI: 75-100%), and with a median follow-up of 6 months OS is not reached.

BV+Ipi+ Nivo (BNI)

In Arm G we have noted one DLT (development of diabetic ketoacidosis in cycle 1). Of the other six patients treated in Arm G, all tolerated their initial triplet therapy and completed cycles 1 and 2 without incidence. In arm H, 6 patients have been successfully treated, with one DLT, transient and asymptomatic grade 3 transminase elevations in cycle 1 in one patient. The patient continued on therapy, the transaminitis did not recur in subsequent cycles. In total 21 patients have been treated with the triplet therapy to date, and, except for one patient who is post AlloBMT who experienced grade 3 rash and reactivation of GVHD after cycle 3, there have been no other significant toxicities, or AEs of note. Among the first 11 response evaluable patients in Arm G and H, there have been 7 complete responses (CRs) to date.

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1.9 Phase II Expansion

In a heavily pretreated relapsed/ refractory HL patient population, 20% of whom had had prior BV and 60% of whom had prior ASCT, the ORR of 72% with a CR rate of 48% for BI and the ORR of of 89% and CR rate of 50% for BN suggests a deepening of response for both doublet combinations compared to single agent BV and N, that may have profound implications for the future therapy of relapsed patients and patients with high risk disease. The CR rate of single agent BV is 34% and that of single agent N is 9%.

The PFS interval to date is short, but a 6 month PFS of 91% for BN suggests encouraging durability particularly in patients with optimal response to therapy. The PFS of BV is 5.6 months and the current phase 2 data demonstrates a PFS for single agent N of approximately 12 months. If the high PFS rate of E4412 is validated, it has the potential to improve outcomes substantially for relapsed and refractory HL and potentially to offer the first treatment regimen outside of initial chemotherapy or stem cell transplant with the potential for long term disease control.

Both doublet regimens appear to have approximately equivalent CR rate in HL, near the 50% threshold. While this is superior to single agent BV and N, there remains substantial room for improvement, with 50% of these young patients who still do not obtain optimal disease control on either doublet regimen. The immunotherapy doublet of N+I has demonstrated higher activity compared to either single agent N or I in melanoma; phase 2 data in patients with BRAF wild-type melanoma that showed objective response rates of 61% with the combination therapy and 11% with the monotherapy, with complete responses in 22% and 0% of patients (67). These results were confirmed in a Phase 3 study which demonstrated superior ORR and PFS for the doublet combination of NI vs single agent N or I (68), albeit with greater toxicity for the doublet regimens.

This study offers us a unique opportunity to develop a paradigm changing treatment platform for relapsed HL. The current Phase 1 design of E4412 with only 9 patients treated at the MTD for both BN and BNI will not provide sufficient

response data to suggest which regimen is superior with respect to both efficacy and safety. Adding a randomized phase 2 component to E4412 will allow us to maximize the use of our existing data, and generate impactful results that have the potential to change the standard of care for patients with relapsed HL. Following this trial, the arm with the higher CR rate and PFS rate, which would be confirmed in this expanded population could be evaluated: i) as a second line therapy randomized against Autologous Stem Cell transplant, a therapy with cure rate of only 50% and significant long term toxicity including infertility and an increased risk of secondary malignancies, or alternately ii) as an upfront strategy in high risk de novo disease randomized against standard of care high dose chemotherapy (BEACOPP or similar). Ultimately our goal in this Phase 2 study is to lay the groundwork for a new treatment standard for patients with relapsed HL. Additionally the substantial correlative studies planned in this Phase 2 expansion will support a deeper understanding of the biologic effects of immunotherapy on responding and non-responding patients, and may help to better understand and precisely tailor these therapies and therapeutic intensity to the patients who are most likely to benefit, and to shape the next generation of immune focused investigations in HL and other lymphoma.

Rev. Add16

1.10 Rationale for Imaging Correlative Study

The introduction of biologic agents exerting their cytotoxic or cytostatic effects through immunologic mechanisms has brought a major therapeutic paradigm shift in the treatment of lymphoma. The response assessment for these agents may require changes in interpretation of imaging studies to account for various cellular responses. The recently adopted Lugano Response Criteria for Lymphoma follows a reading scheme for traditional chemotherapeutic or chemoimmunotherapeutic regimens, primarily incorporating rituximab (Cheson et al, 2014). However, the biologic or immunomodulatory properties of the novel therapeutic agents may cause an early flare phenomenon associated with a subsequent response through activation of natural killer T cells, tumor necrosis factor-α, and other surface molecules causing a significant inflammatory process in the tumor tissue (Goy et al 2013, Witzig et al, 2011, Pro et al 2012). Therefore, it would be clinically beneficial to evaluate various response patterns associated with novel biologic agents to gather data to better guide response profiling for subsequent management. In this trial Ipilumomab (T-lymphocyte-associated (CTLA)-4 monoclonal antibodies), Nivolumab (anti-programmed cell death (PD)-1 monoclonal antibodY) both target immunomodulatory T cells as well as brentuximab vedotin (BV) an antibody drug conjugate (ADC) directed against the CD30 antigen, trigger immune tumoricidal activity. While the reported response rate is high with these combinations, this novel immune-targeted chemotherapy approach, through possible s pseudo progression may render currently available response criteria challenging to apply.

Rev. 9/15 **2. Objectives**

Rev. Add16 2.1 Phase I Objectives:

2.1.1 Primary Objective

To determine the maximum tolerated dose (MTD) and dose limiting toxicities (DLT) of the combinations of brentuximab vedotin and ipilimumab, brentuximab vedotin and nivolumab, and brentuximab vedotin, ipilimumab, and nivolumab.

2.1.2 Secondary Objectives

2.1.2.1 To evaluate complete response (CR) rate, partial response rate (PR) and overall response rate (ORR), for the combinations of brentuximab vedotin and ipilimumab, brentuximab vedotin and nivolumab, and brentuximab vedotin, ipilimumab, and nivolumab.

2.1.2.2 To evaluate the duration of remission (DOR) to these combinations and compare with the DOR achieved with the most recent prior systemic therapy.

2.1.2.3 To evaluate the progression-free survival (PFS) and the overall survival (OS) in patients receiving the combination of brentuximab vedotin and ipilimumab, brentuximab vedotin and nivolumab, and brentuximab vedotin, ipilimumab, and nivolumab.

2.1.3 Correlative Studies

2.1.3.1 To evaluate the ability of these combinations to alter tumor specific T cell immunity.

2.1.3.2 To evaluate the effects of these combinations on systemic immunity

2.1.3.3 To evaluate a panel of cytokine and T cell specific biomarkers from the peripheral blood as a potential immune signature of treatment response to therapy with these combinations for patients with relapsed / refractory HL.

2.1.3.4 To evaluate using gene expression profiling (GEP) a signature of response to these novel combinations of an antibody drug conjugate with immunomodulatory therapy.

Rev. Add16 2.2 Phase II Objectives:

2.2.1 Primary Objective

To evaluate the CR rate for the regimens of brentuximab vedotin and nivolumab compared to brentuximab vedotin, ipilimumab, and nivolumab.

2.2.2 Secondary Objectives

2.2.2.1 To evaluate the ORR, PR, and stable disease (SD) rate for the combinations of brentuximab vedotin and nivolumab and brentuximab vedotin, ipilimumab, and nivolumab.

2.2.2.2 To evaluate the DOR to these combinations and compare with the DOR achieved with the most recent prior systemic therapy.

2.2.2.3 To evaluate the 5 year PFS and OS in patients receiving the combinations of brentuximab vedotin and nivolumab and brentuximab vedotin, ipilimumab, and nivolumab.

2.2.2.4 To further evaluate the safety and characterize the toxicity for the combinations of brentuximab vedotin and nivolumab, and brentuximab vedotin, ipilimumab, and nivolumab.

2.2.3 Correlative Studies

2.2.3.1 To evaluate the ability of these combinations to alter tumor specific T cell immunity, and circulating T cell phenotypes, in patients as a function of treatment response at multiple timepoints during therapy.

2.2.3.2 To evaluate peripheral blood cytokine profiles in responding and resistant patients at multiple timepoints during therapy.

2.2.3.3 To evaluate using GEP a signature of response vs. resistance to these novel combinations of an antibody drug conjugate with immunomodulatory therapy.

2.2.3.4 To evaluate the influence of human gut microbiome dysbiosis on HL lymphomagenesis and the systemic immune response.

2.2.4 Imaging Correlative Studies

2.2.4.1 To evaluate atypical response patterns with currently available response evaluation criteria

2.2.4.2 To correlate response evaluated using currently available response evaluation criteria with duration of response (PFS, EFS, FFS)

2.2.4.3 To evaluate response patterns in different immunotherapy treatment schemes and correlate with historical data using chemotherapy

2.2.4.4 To correlate imaging changes in all treatment schemes quantitatively with PFS

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F) _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration by the treating physician.

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3.1 Phase I - Eligibility Criteria (Arms A, B, C, D, E, F, G, H, I, X, Y, Z)

_____ 3.1.1 Age ≥ 18 years.

_____ 3.1.2 Patients must have pathologically confirmed relapsed or refractory classical Hodgkin Lymphoma (cHL). A biopsy at any relapse is acceptable. Other histologies including lymphocyte predominant (LP) HL are not permitted.

_____ 3.1.3 Patients must have relapsed after first line chemotherapy. May have relapsed after autologous or allogeneic stem cell transplant, or have primary refractory disease. No upper limit for number of prior therapies. If status post allogeneic stem cell transplant, no active graft versus host disease.

_____ 3.1.4 Patients may have received prior brentuximab vedotin, but must not have received brentuximab vedotin within 6 months prior to registration, and must not have relapsed within 6 months of receiving previous brentuximab vedotin. Patients may not have received prior nivolumab or PD1/PDL1 axis agents. Patients in the nivolumab/brentuximab cohorts ONLY (D, E, F, Y) may have received prior ipilimumab.

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_____ 3.1.5 Patients may have received other prior activating immunotherapies (i.e. checkpoint inhibitors), but must not have received them within 6 months prior to registration, and there must be no serious unresolved complication of therapy at the time of registration. For the purposes of this study monoclonal antibodies and antibody drug conjugates are not considered to be activating immunotherapies and there are no additional time restrictions on prior exposure to these agents (except prior brentuximab vedotin).

_____ 3.1.6 ECOG-ACRIN performance status between 0-2.

3.1.7 Patients must have measurable disease as defined in Section 6. Baseline measurements and evaluations must be obtained within 4 weeks of registration to the study. Abnormal PET scans will not constitute evaluable disease unless verified by a diagnostic quality CT scan. Patients must use the same imaging modality (CT or PET/CT) throughout the study.

3.1.8 Women must not be pregnant or breast-feeding due to risk of fetal harm by the chemotherapeutic agents prescribed in this protocol.

All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.

A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female of childbearing potential?_____(Yes or No)

Date of blood or urine test: _____

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3.1.9 Women of childbearing potential (WOCBP) and sexually active males must either abstain from sexual intercourse for the duration of their participation in the study or agree to use both single barrier contraception and birth control pills or implants for at least one week prior to the start of the study drug and continuing for 5 months after the last dose of study drug (for female patients) and for 7 months after the last dose of study drug (for male patients who are sexually active with WOCBP).

Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she (or the participating partner) should inform the treating physician immediately.

3.1.10 Patients must have no evidence of dyspnea at rest and a pulse oximetry > 92% while breathing room air.

3.1.11 Patients must have FEV1/FVC > 60% by pulmonary function test (PFT), unless due to large mediastinal mass from HL. Carbon monoxide diffusion capacity (DLCO), FEV1, and FVC all >50% predicted value. All pulmonary function tests must be obtained within one month prior to registration.

3.1.12 Hematologic parameters (unless due to documented marrow involvement) obtained within 2 weeks prior to registration)

3.1.12.1 ANC $\geq$ 1500/mcL (1.5 x 10^9/L)

3.1.12.2 Platelets $\geq$ 75,000/mcL (75 x 10^9/L)

3.1.13 Liver/Renal function, obtained within 2 weeks prior to registration

3.1.13.1 AST/ALT $\leq$ 2.5 x upper limit of normal (ULN)

_____ 3.1.13.2 Bilirubin ≤ 2 x upper limit of normal (ULN) (unless documented Gilbert's Syndrome, for which Bilirubin ≤ 3 x upper limit of normal (ULN) is permitted)

_____ 3.1.13.3 Calculated creatinine clearance by Cockroft-Gault formula ≥ 30 ml/min

_____ 3.1.14 No evidence of prior malignancy except adequately treated non-melanoma skin cancer, in situ cervical carcinoma or any surgically- or radiation-cured malignancy continuously disease free for ≥ 5 years so as not to interfere with interpretation of radiographic response.

_____ 3.1.15 Patient must have no current or prior history of CNS involvement.

_____ 3.1.16 All prior therapy must have been completed at least 21 days prior to enrollment. No concomitant anti lymphoma therapy, including systemic corticosteroids for the purpose of treatment of lymphoma are allowed. Topical steroids are allowed.

_____ 3.1.17 No history of Steven's Johnson's syndrome, TENs syndrome, or motor neuropathy.

_____ 3.1.18 HIV positive patients are allowed on this study if they have a CD4 count > 400, and are on a stable antiviral regimen. Patients with poorly controlled HIV or other chronic active viral infections will be excluded.

_____ 3.1.19 Patients must not have autoimmune disorders or conditions of immunosuppression that require current ongoing treatment with systemic corticosteroids (or other systemic immunosuppressants), including oral steroids (i.e., prednisone, dexamethasone) or continuous use of topical steroid creams or ointments or ophthalmologic steroids. A history of occasional (but not continuous) use of steroid inhalers is allowed.

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Replacement doses of steroids for patients with adrenal insufficiency are allowed. Patients who discontinue use of these classes of medication for at least 2 weeks prior to initiation of study treatment are eligible if, in the judgment of the treating physician investigator, the patient is not likely to require resumption of treatment with these classes of drugs during the study.

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Exclusion from this study also includes patients with a history of symptomatic autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [e.g., Wegener's Granulomatosis]); motor neuropathy considered of autoimmune origin (e.g., Guillain-Barre Syndrome and Myasthenia Gravis); other CNS autoimmune disease (e.g., Multiple sclerosis). Patients with autoimmune hypothyroid disease or type I diabetes on replacement treatment are eligible.

Treatment with systemic corticosteroids (including oral steroids)?
Yes_____ No _____

Continuous use of topical steroid creams/ointments?
Yes_____No _____

Continuous use of steroid containing inhalers?
Yes_____No _____

Adrenal insufficiency?
Yes_____No _____

Date of last dose of steroid containing medicines: _____

_____3.1.20 Patients must not have grade 2 or greater peripheral sensory neuropathy.

_____3.1.21 Patients must not have NYHA Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia.

_____ 3.1.22 Patients must not have previously existing hypersensitivity to brentuximab vedotin or ipilimumab.

_____3.1.23 Patients must not have a serious medical or psychiatric illness likely to interfere with study participation.

_____3.1.24 Patients must not be participating in any other clinical trial or taking any other experimental medications within 21 days prior to registration.

Rev. Add16 _____3.1.25 Routine vaccinations, including seasonal influenza, should be given at least 2 weeks prior to study treatment. Vaccines are not prohibited on study, but must be given at least 6 weeks after cycle 1 and not within 7 days of treatment.

Rev. Add16 _____3.1.26 Patients registering to Arms D, E, F, G, H, I, X, Y must not currently be smoking tobacco or other substances and must not have smoked within the past 6 months.

_____ _____
Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

Rev. Add16

3.2 Randomized Phase II - Eligibility Criteria (Arms K and L)

_____3.2.1 Age ≥ 18 years.

_____3.2.2 Patients must have pathologically confirmed relapsed or refractory classical Hodgkin Lymphoma (cHL). A biopsy at any relapse is acceptable. Other histologies including lymphocyte predominant (LP) HL are not permitted.

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_____3.2.3 Patients must have relapsed after first line chemotherapy. May have relapsed after autologous stem cell transplant, or have primary refractory disease. No upper limit for number of prior therapies. Patient must not have received a prior allogeneic stem cell transplant (out of risk of reactivation of pulmonary GVHD).

_____3.2.4 Patients may have received prior brentuximab vedotin, but must not have received brentuximab vedotin within 6 months prior to registration, and must not have relapsed within 6 months of receiving previous brentuximab vedotin. Patients may not have received prior nivolumab or PD1/PDL1 axis agents. Patients may not have received prior ipilimumab.

_____ 3.2.5 Patients may not have received other prior activating immunotherapies (i.e. checkpoint inhibitor therapies). For the purposes of this study monoclonal antibodies and antibody drug conjugates are not considered to be activating immunotherapies and there are no additional time restrictions on prior exposure to these agents (except prior brentuximab vedotin).

_____3.2.6 ECOG-ACRIN performance status between 0-2.

_____3.2.7 Patients must have measurable disease as defined in Section 6. Baseline measurements and evaluations must be obtained within 4 weeks of registration to the study. Abnormal PET scans will not constitute evaluable disease unless verified by a diagnostic quality CT scan. Patients must use the same imaging modality (CT or PET/CT) throughout the study.

_____3.2.8 Women must not be pregnant or breast-feeding due to risk of fetal harm by the chemotherapeutic agents prescribed in this protocol.

All females of childbearing potential must have a blood test or urine study within 24 hours prior to enrollment to rule out pregnancy.

A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female of childbearing potential?_____(Yes or No)

Date of blood or urine test: _____

_____3.2.9 Women of childbearing potential (WOCBP) and sexually active males must either abstain from sexual intercourse for the duration of their

participation in the study or agree to use both double barrier contraception and birth control pills or implants for at least one week prior to the start of the study drug and continuing for 5 months after the last dose of study drug (for female patients) and for 7 months after the last dose of study drug (for male patients who are sexually active with WOCBP).

Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she (or the participating partner) should inform the treating physician immediately.

_____3.2.10 Patients must have no evidence of dyspnea at rest and a pulse oximetry > 92% while breathing room air.

_____3.2.11 Patients must have FEV1/FVC > 60% by pulmonary function test (PFT), unless due to large mediastinal mass from HL. Carbon monoxide diffusion capacity (DLCO), FEV1, and FVC all >50% predicted value. All pulmonary function tests must be obtained within one month prior to registration.

_____3.2.12 Hematologic parameters (unless due to documented marrow involvement) obtained within 2 weeks prior to registration)

_____3.2.12.1 ANC $\geq$ 1500/mcL (1.5 x 10^9/L)

_____3.2.12.2 Platelets $\geq$ 75,000/mcL (75 x 10^9/L)

_____3.2.13 Liver/Renal function, obtained within 2 weeks prior to registration

_____3.2.13.1 AST/ALT $\leq$ 2.5 x upper limit of normal (ULN)

_____3.2.13.2 Bilirubin $\leq$ 2 x upper limit of normal (ULN) (unless documented Gilbert's Syndrome, for which Bilirubin $\leq$ 3 x upper limit of normal (ULN) is permitted)

_____3.2.13.3 Calculated creatinine clearance by Cockroft-Gault formula $\geq$ 30 ml/min

_____3.2.14 No evidence of prior malignancy except adequately treated non-melanoma skin cancer, in situ cervical carcinoma or any surgically- or radiation-cured malignancy continuously disease free for $\geq$ 5 years so as not to interfere with interpretation of radiographic response.

_____3.2.15 Patient must have no current or prior history of CNS involvement.

_____3.2.16 All prior therapy must have been completed at least 21 days prior to enrollment (6 weeks for nitrosoureas or mitomycin C). No concomitant anti lymphoma therapy, including systemic corticosteroids for the purpose of treatment of lymphoma are allowed. Topical steroids are allowed.

_____3.2.17 No history of Steven's Johnson's syndrome, TENs syndrome, or motor neuropathy.

_____3.2.18 HIV positive patients are eligible provided they meet the other protocol criteria including the following:

- Long term survival expected were it not for the cHL

- HIV viral loads undetectable by standard clinical HIV testing
- Willing to adhere to effective combination antiretroviral therapy

_____3.2.19 Patients must not have autoimmune disorders or conditions of immunosuppression that require current ongoing treatment with systemic corticosteroids (or other systemic immunosuppressants), including oral steroids (i.e., prednisone, dexamethasone) or continuous use of topical steroid creams or ointments or ophthalmologic steroids. A history of occasional (but not continuous) use of steroid inhalers is allowed.

Replacement doses of steroids for patients with adrenal insufficiency are allowed. Patients who discontinue use of steroid medication for at least 2 weeks prior to initiation of therapy are eligible if, in the judgment of the treating physician investigator, the patient is not likely to require resumption of treatment with these classes of drugs during the study.

Exclusion from this study also includes patients with a history of symptomatic autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [e.g., Wegener's Granulomatosis]); motor neuropathy considered of autoimmune origin (e.g., Guillain-Barre Syndrome and Myasthenia Gravis); other CNS autoimmune disease (e.g., Multiple sclerosis). Patients with autoimmune hypothyroid disease or type I diabetes on replacement treatment are eligible.

Treatment with systemic corticosteroids (including oral steroids)?
Yes_____No _____

Continuous use of topical steroid creams/ointments?
Yes_____No _____

Continuous use of steroid containing inhalers?
Yes_____No _____

Adrenal insufficiency?
Yes_____No _____

Date of last dose of steroid containing medicines: _____

_____3.2.20 Patients must not have grade 2 or greater peripheral sensory neuropathy.

_____3.2.21 Patients must not have NYHA Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia.

_____ 3.2.22 Patients must not have previously existing hypersensitivity to brentuximab vedotin or ipilimumab.

_____3.2.23 Patients must not have a serious medical or psychiatric illness likely to interfere with study participation.

_____ 3.2.24 Patients must not be participating in any other clinical trial or taking any other experimental medications within 21 days prior to registration.

_____3.2.25 Routine vaccinations, including seasonal influenza, should be given at least 2 weeks prior to study treatment. Vaccines are not prohibited on study, but must be given at least 6 weeks after cycle 1 and not within 7 days of treatment.

Rev. Add20 _____3.2.26 Patients must not currently be smoking tobacco or other agents. Vaping is not allowed.

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_____3.2.27 Patients must not have a history of or evidence of cardiovascular risks including any of the following:

- QT interval corrected for heart rate using the Bazett's formula QTcB ≥ 480 msec.at baseline.
- History of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty, or stenting within the past 24 weeks prior to registration.
- History prior to registration or evidence of current ≥ Class II congestive heart failure as defined by the New York Heart Association (NYHA) functional classification system. (See Appendix IX)
- LVEF ≤ lower limit of normal on cardiac echo or MUGA.
- Intra-cardiac defibrillator.
- History of abnormal cardiac valve morphology (≥ grade 2) documented by ECHO; (subjects with grade 1 abnormalities [i.e., mild regurgitation/stenosis] can be entered on study). Subjects with moderate valvular thickening should not be entered on study.
- History or evidence of current clinically significant uncontrolled cardiac arrhythmias; Clarification: Subjects with atrial fibrillation controlled for >30 days prior to dosing are eligible.
- Treatment refractory hypertension defined as a blood pressure of systolic >140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

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4. Registration Procedures

CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

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Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR *Help Desk* by email at <RCRHelpDesk@nih.gov>.

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CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

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Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number

- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

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Downloading Site Registration Documents:

Site registration forms may be downloaded from the E4412 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the ECOG-ACRIN link to expand, then select trial protocol #E4412
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

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Requirements for E4412 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) ❼ Regulatory Tab ❼ Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

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Required Protocol Specific Regulatory Documents

1. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

2. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:

   - Indicate all sites approved for the protocol under an assurance number.
   - OHRP assurance number of reviewing IRB
   - Full protocol title and number
   - Version Date
   - Type of review (full board vs. expedited)
   - Date of review.
   - Signature of IRB official

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Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

NOTE: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7

basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam>) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

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4.1 Phase I - Dose Escalation Registration Procedures (Arms A, B, D, E, G, H, X, Y, and Z)

Registration will be a two step process: slot reservation, followed by registration to treatment (Step 1).

Patients must not start protocol treatment prior to registration to Step 1.

4.1.1 Slot Reservation

Please note that a slot must be reserved prior to starting eligibility verification to receive an update on the accrual and possible suspension status of the study. Slots will automatically EXPIRE after 10 days.

Only after a slot has been reserved should the patient be worked up for the study. If the patient is found to be ineligible, the site must withdraw the slot via the OPEN Registration system. The expired slot will then be made available for reassignment.

The following information will be requested:

4.1.1.1 Protocol Number

4.1.1.2 Investigator Identification

4.1.1.2.1 Institution and affiliate name (Institution CTEP ID)

4.1.1.2.2 Protocol specific contact information

4.1.1.3 Patient Identification

4.1.1.3.1 Patient's initials (first and last)

4.1.1.3.2 Patient demographics

4.1.1.3.2.1 Gender

4.1.1.3.2.2 Birth date (mm/yyyy)

4.1.1.3.2.3 Nine-digit ZIP code

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4.1.2 Registration to Step 1 Treatment - Arms A, B, D, E, G, H, X, Y and Z

Patients must not start protocol treatment prior to registration to Step 1.

Treatment should start within 7 working days after registration.

The following information will be requested at the time of registration to Step 1:

4.1.2.1 Protocol Number

4.1.2.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.1.2.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.1.3 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1.

4.1.4 Additional Requirements

4.1.4.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office - Boston.

4.1.4.2 Pathological/biological samples are to be submitted for central diagnostic review and defined laboratory research studies as indicated in Section 11.

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NOTE: The establishment of research rates within the institution's financial office must be in place prior to the performance of the research biopsies. See Section 11.6 for guidelines.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office - Boston.

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4.1.4.3 Data collection for this study will be done exclusively through Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS. To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA, Lab Admin, SLA, or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

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4.1.5 Instructions for Patients who do Not Start Assigned Protocol Treatment

If a patient registers to Step 1, and does not start therapy, the reason the patient did not start protocol therapy will be collected (no additional data will be collected). If the above scenario occurs please notify the E4412 study team at the ECOG-ACRIN Operations Office – Boston and Study Chair so that an additional patient may be accrued to that cohort to replace the patient who did not receive treatment. If a patient does start therapy and leaves the study prior to completion of 1 cycle of treatment, baseline and follow-up data will still be collected and must be submitted by Medidata Rave according to the schedule in the E4412 Forms Completion Guidelines.

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4.2 Phase I - Dose Expansion Registration Procedures (Arms C, F, and I)

Registration will be a two step process: slot reservation, followed by registration to treatment (Step 1).

Patients must not start protocol treatment prior to registration to Step 1.

4.2.1 Slot Reservation

Please note that a slot must be reserved prior to starting eligibility verification to receive an update on the accrual and possible suspension status of the study. Slots will automatically EXPIRE after 10 days.

Only after a slot has been reserved should the patient be worked up for the study. If the patient is found to be ineligible, the site must withdraw the slot via the OPEN Registration system. The expired slot will then be made available for reassignment.

The following information will be requested:

4.2.1.1 Protocol Number

4.2.1.2 Investigator Identification

4.2.1.2.1 Institution and affiliate name (Institution CTEP ID)

4.2.1.2.2 Protocol specific contact information

4.2.1.3 Patient Identification

4.2.1.3.1 Patient's initials (first and last)

4.2.1.3.2 Patient demographics

4.2.1.3.2.1 Gender

4.2.1.3.2.2 Birth date (mm/yyyy)

4.2.1.3.2.3 Nine-digit ZIP code

4.2.2 Registration to Step 1 Treatment - Arms C, F, and I

Patients must not start protocol treatment prior to registration.

Treatment should start within 7 working days after registration.

The following information will be requested for registration:

4.2.2.1 Protocol Number

4.2.2.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.2.2.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.2.2.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office - Boston.

4.2.3 Additional Requirements

4.2.3.1 Patients must provide a signed and dated, written informed consent form.

Pathological/biological samples are to be submitted for central diagnostic review and defined laboratory research studies as indicated in Section 11.

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NOTE: The establishment of research rates within the institution's financial office must be in place prior to the performance of research biopsies. See Section 11.6 for guidelines.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office - Boston.

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4.2.3.3 Data collection for this study will be done exclusively through Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate

Rave role (Rave CRA, Read-Only, CRA, Lab Admin, SLA, or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

4.2.4 Instructions for Patients who do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted by Medidata Rave according to the schedule in the E4412 Forms Completion Guidelines.

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4.3 Phase II - Registration and Randomization Procedures

Patients must not start protocol treatment prior to randomization.

Treatment must start within seven working days after registration.

Please note that when a patient has been successfully randomized, the confirmation of registration will indicate that the patient is on either arm K or L.

The following information will be requested:

4.3.1 Protocol Number

4.3.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.3.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.3.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.2.

4.3.5 Stratification Factors

Patients will be stratified according to the following factors for purposes of balancing arms:

4.3.5.1 Prior Brentuximab-vedotin (BV) use:

4.3.5.1.1 Prior BV or no prior BV

4.3.6 Additional Requirements

4.3.6.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office - Boston.

4.3.6.2 Pathological/biological samples are to be submitted for central diagnostic review and defined laboratory research studies as indicated in Section 11.

NOTE: The establishment of research rates within the institution's financial office must be in place prior to the performance of the research biopsies. See Section 11.6 for guidelines.

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4.3.7 Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons

with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Rave Read-Only, Rave CRA (Lab Admin), Rave SLA, or Rave Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or RAVE CRA (Lab Admin) role, the user must hold a minimum of an AP registration type. To hold the Rave Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

4.3.8 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted by Medidata Rave according to the schedule in the E4412 Forms Completion Guidelines.

5. Treatment Plan

5.1 Treatment Design – Phase I

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Phase I Dose Escalation treatment will employ a modified 3 + 3 dose escalation schema for the ipilimumab/brentuximab arms, and a standard 3 + 3 dose escalation schema for the nivolumab/brentuximab and nivolumab/ipilimumab/brentuximab arms. Patients will therefore be treated in cohorts of 3 patients starting with Arm A with 1mg/kg of ipilimumab by IV infusion and 1.8 mg/kg of brentuximab vedotin by IV beginning on Day 1. Dose escalation will precede expansion cohort in all instances.

In Arms A, B, and Z if ≤ 1 out of 3 patients at a particular dose level experiences a dose limiting toxicity (DLT) (see Section 5.1.6) within Cycle 1 of treatment, 3 additional patients will be treated at that same dose level. If a DLT occurs in only 1 out of 6 patients enrolled at a particular dose level, dose escalation will occur, however, if this occurs on Arm B (3 mg/kg) or Arm Z (0.3 mg/kg), this will be deemed the Maximum Tolerated Dose (MTD). MTD is defined as the highest dose level at which < 33% of 6 patients experience a DLT.

If a DLT occurs in ≥ 2 of 3 patients or ≥ 2 of 6 patients treated on Arm A (1 mg/kg), there will be a dose de-escalation to Arm Z (0.3 mg/kg).

If a DLT occurs in ≥ 2 of 3 patients or ≥ 2 of 6 patients treated on Arm B (3 mg/kg), the preceding dose level will be declared the MTD if 1 out of 6 DLTs were assessed in this previous cohort.

If a DLT occurs in ≥ 2 of 3 patients or ≥ 2 of 6 patients on Arm Z (0.3 mg/kg), the trial will be discontinued and the expanded cohort will not be implemented.

Arm A: 1 mg/kg ipilimumab + 1.8 mg/kg brentuximab vedotin

Number of Observed DLTs	Action
≤ 1/3	Add 3 more patients to current dose level (Arm A)
≥ 2/3	Deescalate to Arm Z dose level
≤ 1/6	Escalate to Arm B dose level
≥ 2/6	Deescalate to Arm Z dose level

Arm B: 3 mg/kg ipilimumab + 1.8 mg/kg brentuximab vedotin

Number of Observed DLTs	Action
≤ 1/3	Add 3 more patients to current dose level (Arm B)
≥ 2/3	Arm A is MTD
≤ 1/6	Arm B declared as MTD
≥ 2/6	Arm A is MTD

Arm Z: 0.3 mg/kg ipilimumab + 1.8 mg/kg brentuximab vedotin

Number of Observed DLTs	Action
≤ 1/3	Add 3 more patients to current dose level (Arm Z)
≥ 2/3	Discontinue trial
≤ 1/6	Arm Z declared as MTD
≥ 2/6	Discontinue trial

The Maximum Tolerated Dose (MTD) is the highest dose of ipilimumab that can be combined with the standard fixed dose of brentuximab vedotin. A minimum of 6 patients in Arms A, B, and Z (brentuximab/ipilimumab) will be treated at the MTD to obtain sufficient toxicity data prior to enrollment of the expansion cohort.

Once the brentuximab/ipilimumab patients have completed treatment accrual to the nivolumab/brentuximab arms will commence. For the nivolumab/brentuximab and nivolumab/ ipilimumab/brentuximab patients will be treated in cohorts of 3 patients with a standard 3+3 design beginning with Arm D with 3mg/kg of nivolumab and 1.2mg/kg of brentuximab vedotin. Accrual to the combination of brentuximab/ipilimumab/and nivolumab will only occur once all patients have been treated with brentuximab and nivolumab.

If 0 out of 3 patients at a particular dose level experiences a dose limiting toxicity (DLT) (see Section 5.1.6) within Cycle 1 of treatment, dose escalation will occur, however, if this occurs on Arm E or Arm H 3 additional patients will be treated at the same dose level. This will be deemed the Maximum Tolerated Dose (MTD) if no more than 1 of 6 patients experience a DLT.

If a DLT occurs in 1 out of 3 patients, then 3 additional patients will be entered at the same dose level. If a DLT occurs in ≥ 2 of 3 patients treated on Arm D or G,there will be a dose de-escalation to Arm Y (1 mg/kg nivolumab + 1.2 mg/kg brentuximab vedotin) or Arm X (1 mg/kg nivolumab + 1mg/kg ipilimumab + 1.2 mg/kg brentuximab vedotin).

If a DLT occurs in ≥ 2 of 3 patients treated on Arm E or H, the preceding dose level will be declared the MTD if no more than 1 out of 6 treated patients experienced DLT.

If a DLT occurs in ≥ 2 of 3 patients on Arm Y or Arm X, the trial will be discontinued and the expanded cohort will not be implemented.

If 6 patients were treated on a dose level in arm D, arm G and 1 experienced DLT, does escalation will occur. If 6 patients were treated on a dose level (arm D or G) and 2 or more experienced DLT, dose de-escalation will occur. If 6 patients were treated on arm Y or arm X and 2 or more experienced DLT, the trial will be discontinued and the expanded cohort will not be implemented.

For the nivolumab/brentuximab and nivolumab/ ipilimumab/brentuximab, the MTD is defined as the highest dose level at which no more than 1 out of 6treated patients experienced a DLT.

Arm D: 3 mg/kg nivolumab + 1.2 mg/kg brentuximab vedotin

Number of Observed DLTs	Action
0/3	Escalate to Arm E dose level
1/3	Treat next cohort of 3 patients on the current dose level (Arm D)
≥ 2/3	Deescalate to Arm Y
≤ 1/6	Escalate to Arm E dose level; or Arm D declared as MTD if deescalated from Arm E
≥ 2/6	Deescalate to Arm Y dose level

Arm E: 3 mg/kg nivolumab + 1.8 mg/kg brentuximab vedotin

Number of Observed DLTs	Action
≤ 1/3	Add 3 more patients to current dose level (Arm E)
≥ 2/3	Treat a total 6 patients on the preceding dose level (Arm D)
≤ 1/6	Arm E declared as MTD
≥ 2/6	Treat a total 6 patients on the preceding dose level (Arm D)

Arm Y: 1 mg/kg nivolumab + 1.2 mg/kg brentuximab vedotin

Number of Observed DLTs	Action
≤ 1/3	Add 3 more patients to current dose level (Arm Y)
≥ 2/3	Discontinue arm
≤ 1/6	Arm Y declared as MTD
≥ 2/6	Discontinue arm

Arm G: 3 mg/kg nivolumab + 1mg/kg ipilimumab + 1.2 mg/kg brentuximab vedotin

Number of Observed DLTs	Action
0/3	Escalate to Arm H dose level
1/3	Treat next cohort of 3 patients on the current dose level (Arm G)
≥ 2/3	Deescalate to Arm X dose level
≤ 1/6	Escalate to Arm H dose level, or Arm G declared as MTD if deescalated from Arm H.
≥ 2/6	Deescalate to Arm X dose level

Arm H: 3 mg/kg nivolumab + 1mg/kg ipilimumab + 1.8 mg/kg brentuximab vedotin

Number of Observed DLTs	Action
≤ 1/3	Add 3 more patients to current dose level (Arm H)
≥ 2/3	Treat a total 6 patients on the preceding dose level (Arm G)
≤ 1/6	Arm H declared as MTD
≥ 2/6	Treat a total 6 patients on the preceding dose level (Arm G)

Arm X: 1 mg/kg nivolumab + 1mg/kg ipilimumab + 1.2 mg/kg brentuximab vedotin

Number of Observed DLTs	Action
≤ 1/3	Add 3 more patients to current dose level (Arm X)
≥ 2/3	Discontinue arm
≤ 1/6	Arm X declared as MTD
≥ 2/6	Discontinue arm

Expansion cohorts of 9 patients will be accrued at the MTD of brentuximab + nivolumab (Arm F) and brentuximab + nivolumab + ipilimumab (Arm I). Dose escalation will not commence for brentuximab + nivolumab + ipilimumab arms until accrual has completed for the preceding brentuximb + ipilimumab and brentuximab + nivolumab doublet arms. In all cohorts dose escalation will preceed the expansion arms.

Rev. 8/14, 9/15

5.1.1 Treatment Administration Brentuximab + Ipilimumab (Arms A, B, C, and Z)

1 cycle = 21 days

A maximum of 7 doses of ipilimumab and 16 doses of brentuximab vedotin will be given, for a maximum of 16 cycles.

On Day 1 of cycles 1-4 patients will receive brentuximab vedotin IV followed by ipilimumab IV. There should be a 90 minute observation period between the completion of brentuximab vedotin and before therapy with ipilimumab is initiated.

On Day 1 of cycles 8, 12 and 16 patients will receive brentuximab vedotin IV followed by ipilimumab IV. There should be a 90 minute observation period between completing brentuximab vedotin and before therapy with ipilimumab is initiated.

On Day 1 of cycles 5, 6, 7, 9, 10, 11, 13, 14 and 15 patients will receive brentuximab vedotin IV only. If the patient has not experienced ANY brentuximab reactions in prior cycles, they are not required to remain for observation after the completion of brentuximab infusion.

Prior to treatment with brentuximab and ipilimumab patients will receive prophylactic premedication with Pepcid 40mg IV and Benadryl 50mg at every cycle. For patients in cycle 5 and beyond who have had no infusion reactions the Benadryl dose may be lowered to 25mg or omitted per investigator discretion. Acetaminophen 650mg may be included as a premedication per investigator discretion.

5.1.1.1 Administration Schedule Brentuximab + Ipilimumab (Arms A, B, C, and Z)

Treatment will continue until progressive disease (as defined by Section 6.4) or unacceptable toxicity.

Phase I Dose Escalation Cohort

Arm A: Ipilimumab 1 mg/kg IV day 1 cycles 1-4, 8, 12, and 16 for a total of 7 doses

Brentuximab vedotin 1.8 mg/kg IV day 1 cycles 1-16

Arm B: Ipilimumab 3 mg/kg IV day 1 cycles 1-4, 8, 12, and 16 for a total of 7 doses

Brentuximab vedotin 1.8 mg/kg IV day 1 cycles 1-16

Arm Z: Ipilimumab 0.3 mg/kg IV day 1 cycles 1-4, 8, 12, and 16 for a total of 7 doses

Brentuximab vedotin 1.8 mg/kg IV day 1 cycles 1-16

Phase I Expansion Cohort

Arm C: Ipilimumab 3 mg/kg IV day 1 cycles 1-4, 8, 12, and 16 for a total of 7 doses

Brentuximab vedotin 1.8 mg/kg IV day 1 cycles 1-16

5.1.2 Treatment Administration Brentuximab + Nivolumab (Arms D, E, F, and Y)

Rev. 9/15

1 cycle = 21 days (3 weeks) for first 16 doses; from dose 17: 1 cycle = 14 days (2 weeks)

A maximum of 16 doses of brentuximab vedotin will be given, for a maximum of 16 cycles. A maximum of 46 doses of nivolumab will be given for patients who are deriving clinical benefit (SD, PR, CR) without excessive toxicity and do not have a transplant option or other curative therapy, they may remain on nivolumab therapy for up to 46 total doses after completing brentuximab.

On Day 1 of every cycle 1-16 patients will receive brentuximab vedotin IV followed by nivolumab IV. There should be a 30 minute observation period between the completion of brentuximab vedotin and before therapy with nivolumab is initiated. For cycles 1-4, there should be a 30 minute observation period after completion of all therapies. Patients who have not experienced any infusion reactions, are not required to remain for observation following infusion in cycle 5 and beyond.

Rev. 9/16

Beyond cycle 16, or if patients discontinue brentuximab vedotin earlier, patients will receive nivolumab IV alone and cycle length will be 14 days for up 46 doses.

Prior to treatment with brentuximab and nivolumab patients will receive prophylactic premedication with Pepcid 40mg IV and Benadryl 50mg at every cycle. For patients in cycle 5 and beyond who have had no infusion reactions the Benadryl dose may be lowered to 25mg or omitted per investigator discretion. Acetaminophen 650mg may be included as a premedication per investigator discretion. Premedications are not required for patients when receiving nivolumab alone.

5.1.2.1 Administration Schedule Brentuximab + Nivolumab (Arms D, E, F, and Y)

Treatment will continue until progressive disease (as defined by Section 6.4) or unacceptable toxicity, or until 46 doses of nivolumab are completed.

Phase I Dose Escalation Cohort

Arm D: Nivolumab 3 mg/kg IV day 1 cycles 1-16, then 3 mg/kg IV day 1 q 14 days up to for up to 46 doses from start of therapy.

Brentuximab vedotin 1.2 mg/kg IV day 1 up to 16 doses.

Arm E: Nivolumab 3 mg/kg IV day 1 cycles 1- 16, then 3 mg/kg IV day 1 q 14 for up to 46 doses from start of therapy.

Brentuximab vedotin 1.8 mg/kg IV day 1 cycles 1-16

Arm Y: Nivolumab 1 mg/kg IV day 1 cycles 1-16, then 1mg/kg IV day 1 q 14 days for up to 46 doses from start of therapy.

Brentuximab vedotin 1.2 mg/kg IV day 1 cycles 1-16

Phase I Expansion Cohort

Arm F: Nivolumab 3 mg/kg IV day 1 cycles 1- 16, then q 14 days for up to 46 doses from start of therapy.

Brentuximab vedotin 1.8 mg/kg IV day 1 cycles 1-16

5.1.3 Treatment Administration Brentuximab + Nivolumab + Ipilimumab (Arms G, H, I and X)

Rev. 9/15
Rev. 9/16
Rev. 11/16
Rev. 5/17
Rev. Add16

1 cycle = 21 days (3 weeks) for first 16 doses; from dose 17: 1 cycle = 14 days (2 weeks)

A maximum of 9 doses of ipilimumab, and 16 doses of brentuximab vedotin, and 46 doses of nivolumab will be given. A maximum of up to 46 doses of nivolumab will be given for patients who are deriving clinical benefit (SD, PR, CR) without excessive toxicity and do not have a transplant option or other curative therapy.

On day 1 of cycles 1, 5, 9, and 13, patients will receive brentuximab vedotin IV followed by nivolumab IV and ipilimumab IV. There should be a 30 minute observation period between the completion of brentuximab vedotin and before therapy with nivolumab is initiated. Additionally, there should be a 30 minute observation period between the completion of nivolumab and initation of ipilimumab. For cycles 1 and 5, there should be a 30 minute observation period after ipilimumab administration. After cycle 5, a 30 minute observation period after ipilimumab administration is not required.

On day 1 of cycles 2-16 (except for cycles 5, 9, and 13), patients will receive brentuximab vedotin IV followed by nivolumab IV. There should be a 30 minute observation period between the completion of brentuximab vedotin and initation of nivolumab therapy. There is no 30 minute observation period required after administration of nivolumab.

Beyond cycle 16, or if brentuximab vedotin therapy is discontinued earlier, patients will receive nivolumab IV and ipilimumab IV and cycle length will be 14 days for up to 46 doses of nivolumab. Ipilimumab will continue to be administered for every 12 weeks for up to 9 doses. Therefore, if brentuximab vedotin is administered for 16 cycles, patients will receive nivolumab and ipilimumab together on day 1 of cycles 17, 23, 29, 35, and 41.

If patients discontinue brentuximab vedotin prior to 16 doses, then the cycle schedule will switch to 1 cycle = 14 days and ipilimumab and nivolumab will be administered per protocol. If brentuximab is discontinued before cycle 16, no observation period post dosing is required. No observation period is required post therapy for beyond cycle 16.

Prior to treatment with brentuximab and ipilimumab, patients will receive prophylactic premedication with Pepcid 40mg IV and Benadryl 50mg at every cycle. For patients in cycle 5 and beyond who have had no infusion reactions the Benadryl dose may be lowered to 25mg or omitted per investigator discretion. Acetaminophen 650mg may be included as a premedication per investigator discretion. Hydrocortisone 100mg or other corticosteroids may be included as a premedication per investigator discretion.

Rev. 5/17, Add16

5.1.3.1 Administration Schedule Brentuximab + Nivolumab + Ipilimumab (Arms G, H, I and X)

Treatment will continue until progressive disease (as defined by Section 6.4) or unacceptable toxicity, or until 46 doses of nivolumab are completed.

Phase I Dose Escalation Cohort

Arm G: Ipilimumab 1 mg/kg IV day 1 beginning cycle 1, every 12 weeks for up to 9 doses from start of therapy

Nivolumab 3mg/kg day 1 cycles 1- 16, then 3mg/kg IV day 1 q 14 for up to 46 doses from start of therapy

Brentuximab vedotin 1.2 mg/kg IV day 1 cycles 1-16

Arm H: Ipilimumab 1 mg/kg IV day 1 beginning cycle 1, every 12 weeks for up to 9 doses from start of therapy

Nivolumab 3 mg/kg IV day 1 cycles 1- 16, then 1mg/kg IV day 1 q 14 for up to 46 cycles from start of therapy

Brentuximab vedotin 1.8 mg/kg IV day 1 cycles 1-16

Arm X: Ipilimumab 1.0 mg/kg IV day 1 beginning cycle 1, every 12 weeks for up to 9 doses from start of therapy

Nivolumab 1mg/kg day 1 cycles 1- 16, then 1mg/kg IV day 1 q 14 for up to 46 cycles from start of therapy

Brentuximab vedotin 1.2 mg/kg IV day 1 cycles 1-16

Phase I Expansion Cohort

Arm I: Ipilimumab 1 mg/kg IV day 1 beginning cycle 1, every 12 weeks for up to 9 doses from start of therapy

Nivolumab 3 mg/kg IV day 1 cycles 1- 16, then 1mg/kg IV day 1 q 14 for up to 46 cycles from start of therapy

Brentuximab vedotin 1.8 mg/kg IV day 1 cycles 1-16

Rev. 11/17

Rev. 9/16
Rev. 5/17
Rev. Add16

5.1.4 Nivolumab with Ipilimumab

When infusions of ipilimumab and nivolumab are given on the same day, the preferred treatment is to give nivolumab followed by ipilimumab.

Toxicity management for the combined agents follows the same template guidelines and algorithms that are provided in Appendix VIII through Appendix XIV for single agent nivolumab.

Follow the same infusion timing guidelines: nivolumab over 30 minutes followed by a 30 minutes observation period and ipilimumab over 30 minutes followed by a 30 minutes observation period. Assuming discontinuation of brentuximab vedotin, the dosing schedule will be q2 weeks for nivolumab and q12 weeks for the nivolumab-ipilimumab combination for patients who continue treatment beyond one year. Number of cycles of nivolumab can add up to 46 cycles of treatment and number of cycles of ipilimumab can add up to 9 doses of treatment. When the patient is not receiving brentuximab vedotin, there is no post observation period required for cycles when only nivolumab is administered. However, for cycles where both nivolumab and ipilimumab are both administered, nivolumab should be followed by a 30 minute observation period prior to ipilimumab infusion through cycle 4. From cycle 5 onwards, no observation is required between nivolumab and ipilimumab.

When both nivolumab and ipilimumab are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion.

5.1.5 Evaluable for Adverse Events

Patients must be evaluated for adverse events on a weekly basis during the first cycle of treatment.

Any patient who receives any study agent will be evaluable for adverse events.

Any patient who experiences a dose-limiting toxicity (DLT) during protocol therapy is considered fully evaluable for adverse events.

If a patient is without toxicity and leaves the study prior to completion of 1 cycle of treatment (and does not undergo a post-cycle 1 assessment), please notify the E4412 study team at the ECOG-ACRIN Operations Office - Boston and Study Chair. Assessment of

toxicity requires 3 patients at a time per cohort, and therefore an opening for a replacement must be made. A total of 6 patients per cohort are required to confirm the MTD for ipilimumab and/or nivolumab with brentuximab vedotin.

Patients will be monitored for adverse events on an ongoing basis throughout the duration of the study.

5.1.6 Dose-Limiting Toxicity (DLT)

Rev. 9/16

A DLT is defined by the occurrence of any of the following toxicities (CTCAE v.4) within the first cycle of treatment of dose escalation cohorts, which is possibly, probably, or definitely related to ipilimumab, nivolumab and/or brentuximab vedotin in order to evaluate potential toxicity related treatment delays or any event within the first cycle of treatment that requires permanent discontinuation of nivolumab, ipilimumab, and/or brentuximab

Non-Hematological dose-limiting toxicity

Any Grade 3 or Grade 4 non-hematological toxicity that is possibly, probably or definitely attributable to the regimen of ipilimumab, nivolumab and/or brentuximab vedotin or ipilimumab and/or brentuximab vedotin is considered a DLT, including the following:

- Non-hematologic toxicity that causes a delay of >14 days in initiating cycle 2.
- Any type of grade 3-4 hypersensitivity reaction (i.e.: allergic reaction, anaphylaxis, serum sickness, skin disorders, etc.), regardless of attribution, that necessitate discontinuation of study drug.
- Any type of grade 3-4 immune related adverse event including skin reactions.
- Grade 3 or greater colitis and bowel perforation
- Grade 3 ALT/AST elevation or 10 x ULN
- Grade 3-4 pneumonitis

The following events are exclusions and are NOT considered a DLT for this protocol, regardless of attribution or specific type:

- Grade 3 nausea, vomiting, diarrhea, or oral mucositis with < 3 days duration
- Grade 3 fever
- Grade 3 infection
- Grade 3 peripheral sensory neuropathy that is decreased by at least one grade within 7 days
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive (i.e.: decreased by at least one grade) to oral supplementation within 7 days
- Grade 3 hypertriglyceridemia that returns to < Grade 2 prior to the beginning of cycle 2

- Grade 3 hyperglycemia that returns to < Grade 2 (with or without the use of insulin or oral diabetic agents) prior to the beginning of cycle 2

Hematological dose-limiting toxicity

The following hematological toxicity possibly, probably or definitely attributable to the regimen of ipilimumab, nivolumab and/or brentuximab vedotin is considered a DLT (except in cases of documented bone marrow infiltration by HL which may be attributed to disease, and which will be discussed on a case by case basis) and must be reported initially via CTEP-AERS within 24 hours, followed by a complete report via CTEP-AERS within 5 calendar days. Growth factors are allowed per treating investigator's discretion in patients at high risk for febrile neutropenia.

- Grade 4 neutropenia for > 7 days

  NOTE: Grade 4 febrile neutropenia will not be a dose-limiting toxicity but should warrant growth factor support on subsequent doses.

- Platelet count < 25,000/uL on 2 separate days, or requiring a platelet transfusion on 2 separate days within a 7 day period
- Myelosuppression that causes a delay of > 14 days in initiating cycle 2

Rev. Add16

5.2 Treatment Design – Phase II

The Phase II design will be a randomized Phase 2 study between Brentuximab-Nivo (BN) and Brentuximab-Ipi-Nivo (BNI). Patients will be randomized at 1:1 ratio to BN or BNI arms, stratifying by prior brentuximab vedotin use (prior BV vs. no prior BV).

5.2.1 Treatment Administration Brentuximab + Nivolumab (Arm K)

1 cycle = 21 days

A maximum of 16 doses of brentuximab vedotin will be given, for a maximum of 16 cycles. A maximum of 34 doses of nivolumab (2 years) will be given for patients who are deriving clinical benefit (SD, PR, CR, IR) without excessive toxicity. Patients who do not have a transplant or other curative therapy option may remain on nivolumab therapy for up to 1 year or 17 further doses after completing brentuximab.

On day 1 of every cycle 1-16, patients will receive brentuximab vedotin IV followed by nivolumab IV. There should be a 30 minute observation period between the completion of brentuximab vedotin and before therapy with nivolumab is initiated. For cycles 1-5, there should be a 30 minute observation period after completion of all therapies. Patients who have not experienced any infusion reactions, are not required to remain for observation following infusion in cycle 5 and beyond.

Beyond cycle 16, or if patients discontinue brentuximab vedotin earlier, patients will receive nivolumab IV alone and cycle length will remain 21 days for up 34 doses.

Prior to treatment with brentuximab and nivolumab, patients will receive prophylactic premedication with Pepcid 40mg IV and Benadryl 50mg at every cycle. For patients in cycle 5 and beyond who have had no infusion reactions, the Benadryl dose may be lowered to 25mg or omitted per investigator discretion. Acetaminophen 650mg may be included as a premedication per investigator discretion. Corticosteroid premedications are allowed per investigator discretion for patients who had prior infusion reactions. Premedications are not required for patients when receiving nivolumab alone.

Arm K: Nivolumab 360mg IV day 1 cycles 1- 34

Brentuximab vedotin 1.8 mg/kg IV day 1 cycles 1-16

5.2.2 Treatment Administration Brentuximab + Nivolumab + Ipilimumab (Arm L)

1 cycle = 21 days

A maximum of 9 doses of ipilimumab, 16 doses of brentuximab vedotin, and 34 doses of nivolumab will be given. A maximum of up to 34 doses of nivolumab will be given for patients who are deriving clinical benefit (SD, PR, CR, IR) without excessive toxicity and do not have a transplant option or other curative therapy.

Rev. Add19

On day 1 of cycles 1, 5, 9, and 13, patients will receive brentuximab vedotin IV followed by nivolumab IV (over 30 minutes) and ipilimumab IV (over 30 minutes). There should be a 30 minute observation period between the completion of brentuximab vedotin and before therapy with nivolumab is initiated. Additionally, there should be a 30 minute observation period between the completion of nivolumab and initation of ipilimumab. For cycles 1 and 5, there should also be a 30 minute observation after ipilimumab administration. After cycle 5, a 30 minute observation period after ipilimumab administration is not required.

On day 1 of cycles 2-16 (except for cycles 5, 9, and 13), patients will only receive brentuximab vedotin IV followed by nivolumab IV. There should be a 30 minute observation period between the completion of brentuximab vedotin and initation of nivolumab therapy. There is no 30 minute observation period required after administration of nivolumab.

Beyond cycle 16, patients will receive nivolumab IV and ipilimumab IV and cycle length will be 21 days for up to a total 34 doses of nivolumab. Ipilimumab will continue to be administered every 12 weeks for up to a total 9 doses. Therefore, after brentuximab vedotin is administered for 16 cycles and discontinued, patients will receive nivolumab on day 1 of every cycle and nivolumab and ipilimumab together on day 1 of cycles 17, 21, 25, 29, and 33.

If brentuximab is discontinued before cycle 16, no observation period post dosing is required. No observation period is required post therapy for beyond cycle 16.

Prior to treatment with brentuximab, nivolumb, and ipilimumab, patients will receive prophylactic premedication with Pepcid 40mg IV and Benadryl 50mg at every cycle. For patients in cycle 5 and beyond who have had no infusion reactions, the Benadryl dose may be lowered to 25mg or omitted per investigator discretion. Acetaminophen 650mg may be included as a premedication per investigator discretion. Corticosteroid premedications are allowed per investigator discretion for patients who have had prior infusion reactions. Patients who are no longer receiving brentuximab vedotin do not need to receive Benadryl premedication.

Rev. Add20

Arm L: Ipilimumab 1 mg/kg IV day 1 beginning cycle 1, every 12 weeks for up to 9 doses from start of therapy

Nivolumab 360mg day 1 cycles 1- 34

Brentuximab vedotin 1.8 mg/kg IV day 1 cycles 1-16

Rev. 5/14

5.3 Adverse Event Reporting Requirements

NOTE: Starting April 1, 2018, all expedited adverse events reporting through CTEP-AERS must use CTCAE v5, regardless of phase. The Phase II portion of the study utilizes CTCAE v5 for routing reporting of adverse events in Rave, while the Phase I portion of the study will continue to utiltize CTCAE v4 for routine adverse event reporting in Rave.

Rev. Add21

5.3.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

1. **Routine reporting**: Adverse events are reported in a routine manner at scheduled times during a trial using Medidata Rave.
2. **Expedited reporting**: In addition to routine reporting, certain adverse events must be reported in an expedited manner via CTEP-AERS for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

5.3.2 Terminology

1. **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to treatment.
Unlikely	The AE is *doubtfully related* to treatment.
Possible	The AE *may be related* to treatment.
Probable	The AE is *likely related* to treatment.
Definite	The AE is *clearly related* to treatment.

Rev. 5/14

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.

Rev. Add16

- **Dose Limiting Toxicity (DLT):** The appearance of side effects during the first cycle of treatment that are possibly severe enough to prevent further increase in dosage or strength of treatment agent, or to prevent continuation of treatment at any dosage level. Any adverse event occurring on the phase I portion of the study that meets the E4412 definition of DLT must be reported via CTEP-AERS.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥24 hours).
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  - A congenital anomaly/birth defect.
  - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Rev. 1/15

- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains a list of events that are protocol specific exceptions to expedited reporting. Please see Section 5.4 for further instructions on the use of the SPEER in this protocol.

5.3.3 Reporting Procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

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1. the AE Team at ECOG-ACRIN (857-504-2900)
2. the NCI (301-897-7497)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301- 230-0159) in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.3.4 Determination of Reporting Requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

1. the phase (0, 1, 2, or 3) of the trial
2. whether the patient has received an investigational or commercial agent or both
3. the seriousness of the event
4. the Common Terminology Criteria for Adverse Events (CTCAE) grade
5. whether or not hospitalization or prolongation of hospitalization was associated with the event
6. when the adverse event occurred (within 30 days of the last administration of investigational agent vs. ≥ 30 days after the last administration of investigational agent)
7. the relationship to the study treatment (attribution)

Using these factors, the instructions and tables in the following sections have been customized for protocol E4412 and outline the

specific expedited adverse event reporting requirements for study E4412.

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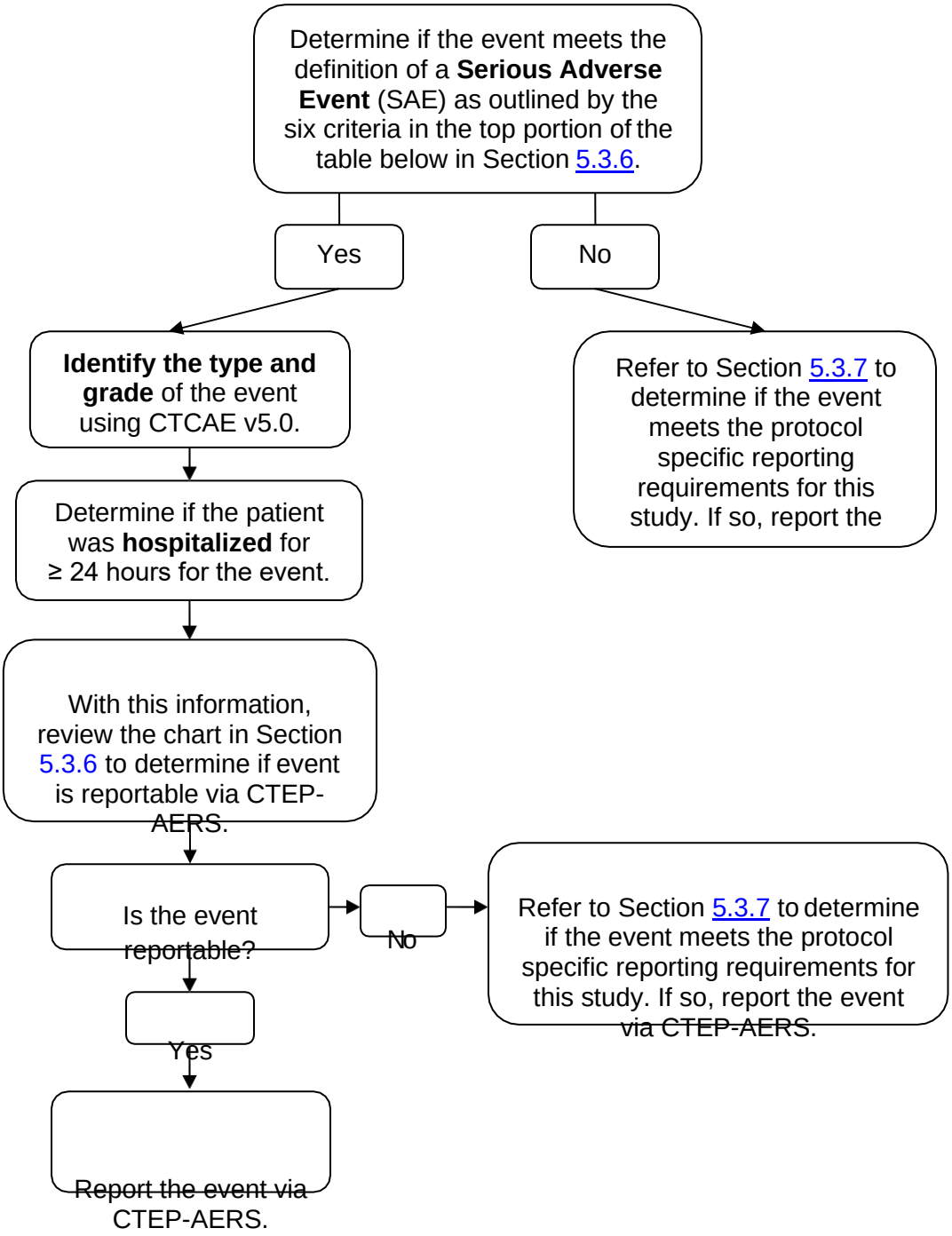
5.3.5 Steps to determine if an adverse event is to be reported in an expedited manner – Arms A, B, D, E, G, H, X, Y, Z, C, F, I, K, and L

5.3.5.1 Guidelines for adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).



5.3.5.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event (SAE)** as outlined by the six criteria in the top portion of the table below in Section 5.3.6, AND has an attribution of possible, probably or definite, the following events require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported via CTEP-AERS even if the patient is off study.

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization

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5.3.6 Expedited Reporting Requirements for Arms A, B, D, E, G, H, X, Y, Z, C, F, I, K, and L on protocol E4412

Investigational Agents: Ipilimumab, Nivolumab

Commercial Agents: Brentuximab Vedotin

When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events follow the guidelines for investigational agents.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

Effective Date: May 5, 2011

5.3.7 Additional instructions, requirements and exceptions for protocol E4412

Additional Instructions:

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

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- **Reporting a death on study**: A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

  NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

E4412 specific expedited reporting requirements:

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Phase I Only (Arms A, B, D, E, G, H, X, Y, Z, C, F, and I)

- **Dose Limiting Toxicities (DLTs).** The following events require expedited reporting via CTEP-AERS.

  NOTE: In order to avoid unnecessary queries, please be sure to include all relevant details in the 'Description of Event' and/or 'Abnormal or Relevant Normal Lab values' sections of the CTEP-AERS report so that the ECOG-ACRIN Operations Office can document that the adverse event meets the definitions of DLT below (i.e: duration, grade, relevant lab values, etc).

  A DLT is defined by the occurrence of any of the following toxicities (CTCAE v.4) within the first cycle of treatment which is possibly, probably, or definitely related to ipilimumab, nivolumab and/or brentuximab vedotin in order to evaluate potential toxicity related treatment delays or any event within the first cycle of treatment that requires permanent discontinuation of nivolumab, ipilimumab, and/or brentuximab:

  Non-Hematological dose-limiting toxicity

Any Grade 3 or Grade 4 non-hematological toxicity that is possibly, probably or definitely attributable to the regimen of ipilimumab, nivolumab and/or brentuximab vedotin ipilimumab and/or brentuximab vedotin is considered a DLT and must be reported initially via CTEP-AERS within 24 hours, followed by a complete report via CTEP-AERS within 5 calendar days, including the following:

- Non-hematologic toxicity that causes a delay of >14 days in initiating cycle 2
- Any type of grade 3-4 hypersensitivity reaction (i.e.: allergic reaction, anaphylaxis, serum sickness, skin disorders, etc.), regardless of attribution, that necessitate discontinuation of study drug.
- Any type of grade 3-4 immune related adverse event including skin reactions. Please submit any supporting data as well (ie: autoimmune serology tests or biopsy reports)
- Grade 3 or greater colitis and bowel perforation
- Grade 3 ALT/AST elevation
- Grade 3-4 pneumonitis

The following non-hematological events are exclusions and are **NOT** considered a DLT for this protocol, regardless of attribution or specific type:

- Grade 3 nausea, vomiting, diarrhea, or oral mucositis with < 3 days duration
- Grade 3 fever
- Grade 3 infection
- Grade 3 peripheral sensory neuropathy that is decreased by at least one grade within 7 days
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive (i.e.: decreased by at least one grade) to oral supplementation within 7 days
- Grade 3 hypertriglyceridemia that returns to < Grade 2 prior to the beginning of cycle 2
- Grade 3 hyperglycemia that returns to < Grade 2 (with or without the use of insulin or oral diabetic agents) prior to the beginning of cycle 2

<u>Hematological dose-limiting toxicity</u>

The following hematological toxicity that is possibly, probably or definitely attributable to the regimen of brentuximab vedotin with ipilumumab and/or nivolumab is considered a DLT (except in cases of documented bone marrow infiltration by HL which may be attributed to disease, and which will be discussed on a case-by-case basis) and must be reported initially via CTEP-AERS within 24 hours, followed by a complete report via CTEP-AERS within 5 calendar days.

~~Growth factors are allowed per treating investigator's~~ discretion in patients at high risk for febrile neutropenia.

- Grade 4 neutropenia for > 7 days

  NOTE: Grade 4 febrile neutropenia will not be a dose-limiting toxicity, and therefore not reportable via CTEP-AERS, but should warrant growth factor support on subsequent doses.

- Platelet count < 25,000/uL on 2 separate days, or requiring a platelet transfusion on 2 separate days within a 7 day period
- Myelosuppression that causes a delay of > 14 days in initiating cycle 2

Phases I and II (Arms A, B, D, E, G, H, X, Y, Z, C, F, I, K and L):

- **Pregnancy**

  Pregnancies and suspected pregnancies (including a positive/inconclusive pregnancy test regardless of age or disease state) occurring while the subject is on ipilimumab, nivolumab and/or brentuximab vedotin, or within 28 days of the subject's last dose of ipilimumab, nivolumab and/or brentuximab vedotin, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. Please refer to Appendix V for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

  - **Infusion Reactions**

    Any grade 3 or 4 infusion reaction that meets the SAE definition (see Section 5.3.2) must be reported via CTEP-AERS within 24 hours, followed by a complete report via CTEP-AERS within 5 calendar days.

  - **Immune Related Adverse Events:** Any grade 3 or higher immune related adverse event (see Section 5.5.1.3 for definition) must be reported via CTEP-AERS in the timeframe outlined in the Section 5.3.6 chart for the specific grade being reported. Please submit any supporting data as well (i.e.: autoimmune serology tests or biopsy reports).

    NOTE: In order for ECOG-ACRIN to appropriately report these events to regulatory agencies, please be sure to state that the event being reported is an IRAE in the 'Description of Event' section of the CTEP-AERS report

Phase II Only (Arms K and L):

- **The adverse events listed below do not require expedited reporting via CTEP-AERS:**

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- Asymptomatic transient elevations of hepatic enzymes, ALT and AST, that resolved to grade 1 or lower within 14 days or less.
- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event. If the protocol uses multiple investigational agents and has an AE listed on multiple SPEERs, use the lower of the grade to determine if expedited reporting is required.

5.3.8 Other recipients of adverse event reports and supplemental data

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to the FDA. Any additional written AE information requested by ECOG-ACRIN MUST be submitted to BOTH the NCI and ECOG-ACRIN.

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

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5.3.9 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require *ONLY routine reporting* as follows**:
  1. Complete a Second Primary Form within 14 days in Medidata Rave.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A secondary malignancy is acancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require *both routine and expedited reporting* as follows:**
  1. Complete a Second Primary Form within 14 days in Medidata Rave.

2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov
    - Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

Rev. 12/14, Add18

5.4 Comprehensive Adverse Events and Potential Risks list (CAEPR)

5.4.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for SGN-35 (brentuximab vedotin, NSC 749710)

Rev. Add21

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Frequency is provided based on 798 patients. Below is the CAEPR for SGN-35 (brentuximab vedotin).

Version 2.5, February 13, 2019[1]

Adverse Events with Possible Relationship to SGN-35 (brentuximab vedotin) (CTCAE 5.0 Term) [n= 798]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
		Febrile neutropenia
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
		Colitis[2]
	Constipation	
Diarrhea		
		Enterocolitis
		Gastrointestinal hemorrhage[3]
		Gastrointestinal obstruction[4]
		Gastrointestinal perforation[5]
		Gastrointestinal ulcer[6]
		Ileus
Nausea		
		Pancreatitis
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
	Edema limbs	
Fatigue		
	Fever	
	Pain	
HEPATOBILIARY DISORDERS		
	Hepatobiliary disorders - Other (hepatotoxicity)[7]	
IMMUNE SYSTEM DISORDERS		
		Anaphylaxis
INFECTIONS AND INFESTATIONS		
	Lung infection	
	Upper respiratory infection	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
		Infusion related reaction
INVESTIGATIONS		

Adverse Events with Possible Relationship to SGN-35 (brentuximab vedotin) (CTCAE 5.0 Term) [n= 798]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Alanine aminotransferase increased	
	Aspartate aminotransferase increased	
Neutrophil count decreased		
	Platelet count decreased	
	Weight loss	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Hyperglycemia	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Muscle cramp	
	Myalgia	
	Pain in extremity	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
		Nervous system disorders - Other (progressive multifocal leukoencephalopathy)
	Paresthesia	
	Peripheral motor neuropathy	
Peripheral sensory neuropathy		
PSYCHIATRIC DISORDERS		
	Anxiety	
	Insomnia	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
	Oropharyngeal pain	
		Respiratory, thoracic and mediastinal disorders - Other (pulmonary toxicity)[8]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Hyperhidrosis	
	Pruritus	
	Rash maculo-papular	
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Colitis may also include the term neutropenic colitis.

[3]Fatal and/or serious gastrointestinal hemorrhages have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[4] Fatal and/or serious gastrointestinal obstructions have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal obstruction includes Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5] Fatal and/or serious gastrointestinal perforations have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC. Lymphoma with preexisting GI involvement may increase the risk of perforation.

[6] Fatal and/or serious gastrointestinal ulcers have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal ulcer includes Anal ulcer, Colonic ulcer, Duodenal ulcer, Esophageal ulcer, Gastric ulcer, Ileal ulcer, Jejunal ulcer, Rectal ulcer, and Small intestine ulcer under the GASTROINTESTINAL DISORDERS SOC.

[7] Hepatotoxicity may manifest as increased ALT/AST, bilirubin, alkaline phosphatase, and/or GGT.

[8] Pulmonary toxicity, which may manifest as pneumonitis, interstitial lung disease, or adult respiratory distress syndrome (ARDS), has been observed in patients treated in brentuximab vedotin monotherapy trials as well as in combination with bleomycin.

Adverse events reported on SGN-35 (brentuximab vedotin) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that SGN-35 (brentuximab vedotin) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (lymphadenopathy)

CARDIAC DISORDERS - Myocardial infarction; Pericardial effusion; Sinus tachycardia

GASTROINTESTINAL DISORDERS - Dyspepsia; Esophagitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Non-cardiac chest pain

INFECTIONS AND INFESTATIONS - Meningitis; Pharyngitis; Sepsis; Shingles; Sinusitis; Skin infection; Soft tissue infection; Thrush; Urinary tract infection

INVESTIGATIONS - Blood lactate dehydrogenase increased; Carbon monoxide diffusing capacity decreased; Creatinine increased; Lipase increased; Lymphocyte count decreased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Myositis; Neck pain

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Myelodysplastic syndrome

NERVOUS SYSTEM DISORDERS - Dysesthesia; Encephalopathy; Nervous system disorders - Other (demyelinating polyneuropathy); Seizure; Syncope

PSYCHIATRIC DISORDERS - Depression

RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (pyelonephritis)

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Reproductive system and breast disorders - Other (groin pain)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome[8]; Pleural effusion[8]; Pneumothorax[8]; Productive cough; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (bronchitis)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin

VASCULAR DISORDERS - Hot flashes; Hypertension; Hypotension; Thromboembolic event

NOTE: SGN-35 (brentuximab vedotin) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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Rev. 1/15
Rev. 3/15
Rev. Add19

5.4.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Ipilimumab (MDX-010, NSCs 732442 and 720801)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 2678 patients. Below is the CAEPR for Ipilimumab (MDX-010).

Rev. Add16

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER. For arms X, G, H, I, and L since these arms use multiple investigational agents, if an AE is listed on both the Ipilimumab and Nivolumab SPEERS, use the lower of the grades to determine if expedited reporting is required.

NOTE: For the phase I portion of this study only, although they appear in the SPEER list as exceptions to expedited reporting**, the following events must be reported via CTEP-AERS** because they meet the E4412 definition of a dose limiting toxicity (see Section 5.3.7):

1. Grade 3-4 colitis (if possibly, probably or definitely related)
2. Grade 3-4 immune related adverse event including skin reactions (if possibly, probably or definitely related)
3. Any 3-4 non hematologic events (if possibly, probably or definitely related) that causes a delay in treatment

Rev. 11/14, 2/17

Version 2.10, March 29, 2019[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (acquired hemophilia)	

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Myocarditis[2]	
		Pericardial effusion	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Hyperthyroidism[2]		
	Hypophysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
	Testosterone deficiency[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2]		
	Uveitis[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		***Colitis[2] (Gr 3)***
		Colonic perforation[3]	
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Enterocolitis		
	Esophagitis		
		Ileus	
Nausea			***Nausea (Gr 3)***
	Pancreatitis[2]		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
		General disorders and administration site conditions - Other (Systemic inflammatory response syndrome [SIRS])	
		Multi-organ failure	
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatitis)[2]		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder[2]		
		Immune system disorders - Other (GVHD in the setting of allotransplant)[4]	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (aseptic meningitis)[2]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
		Lymphocyte count decreased	
	Neutrophil count decreased		
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
	Hyperglycemia		
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
		Generalized muscle weakness	
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		
NERVOUS SYSTEM DISORDERS			
		Ataxia	
	Facial nerve disorder[2]		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Guillain-Barre syndrome[2]		
	Headache		
	Myasthenia gravis[2]		
		Nervous system disorders - Other (immune-mediated encephalitis)[2]	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
	Trigeminal nerve disorder		
PSYCHIATRIC DISORDERS			
		Psychiatric disorders - Other (mental status changes)	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		
		Respiratory failure	
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)	
		Respiratory, thoracic and mediastinal disorders - Other (lung infiltration)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
	Urticaria		
VASCULAR DISORDERS			
	Hypotension		

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis, iritis, conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional treatments.

[3] Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.

[4] Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT.

[5] In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

[6] Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[7] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on ipilimumab (MDX-010) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that ipilimumab (MDX-010) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[2]; Febrile neutropenia

CARDIAC DISORDERS - Conduction disorder; Restrictive cardiomyopathy

EYE DISORDERS - Extraocular muscle paresis[5]; Eye disorders - Other (retinal pigment changes)

GASTROINTESTINAL DISORDERS - Colonic ulcer; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage[6]; Proctitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain

HEPATOBILIARY DISORDERS - Hepatic failure[2]

IMMUNE SYSTEM DISORDERS - Allergic reaction

INFECTIONS AND INFESTATIONS - Infection[7]

INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Dizziness; Dysphasia; Ischemia cerebrovascular; Seizure

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia

RENAL AND URINARY DISORDERS - Proteinuria

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Cough; Dyspnea; Laryngospasm

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Skin hypopigmentation

VASCULAR DISORDERS - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

NOTE: Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Rev. 9/15, 3/16, 2/17
Rev. Add19

5.4.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for BMS-936558 (Nivolumab, MDX-1106, NSC 748726)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2069 patients.* Below is the CAEPR for BMS-936558 (Nivolumab, MDX-1106).

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NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER. For arms X, G, H, I, and L since these arms use multiple investigational agents, if an AE is listed on both the Ipilimumab and Nivolumab SPEERS, use the lower of the grades to determine if expedited reporting is required.

Rev. Add19

NOTE: For the phase I portion of this study only, although they appear in the SPEER list as exceptions to expedited reporting, **the following events must be reported via CTEP-AERS** because they meet the E4412 definition of a dose limiting toxicity (see Section 5.3.7):

1. Grade 3 ALT/AST elevation

Version 2.3, June 18, 2018[1]

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	
		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[3]		
	Hypophysitis[3]		
	Hyperthyroidism[3]		

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypothyroidism[3]		
EYE DISORDERS			
		Blurred vision	
		Dry eye	
		Eye disorders - Other (diplopia)[3]	
		Eye disorders - Other (Graves ophthalmopathy)[3]	
		Eye disorders - Other (optic neuritis retrobulbar)[3]	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[3]		
		Colonic perforation[3]	
	Diarrhea		***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
		Autoimmune disorder[3]	
		Cytokine release syndrome[5]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]	
		Immune system disorders - Other (sarcoid granuloma)[3]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[7]		
INVESTIGATIONS			
	Alanine aminotransferase increased[3]		***Alanine aminotransferase increased[3] (Gr 3)***
	Aspartate aminotransferase increased[3]		***Aspartate aminotransferase increased[3] (Gr 3)***
	Blood bilirubin increased[3]		***Blood bilirubin increased[3] (Gr 2)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)[3]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy[3]	
		Facial nerve disorder[3]	
		Guillain-Barre syndrome[3]	
		Myasthenia gravis[3]	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis)[3]	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis)[3]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome[3]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury[3]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion[3]		
	Pneumonitis[3]		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)[3]	

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme[3]	
	Pruritus[3]		***Pruritus[3] (Gr 2)***
	Rash maculo-papular[3]		***Rash maculo-papular[3] (Gr 2)***
		Skin and subcutaneous disorders -Other (bullous pemphigoid)	
	Skin and subcutaneous disorders - Other (Sweet's Syndrome)[3]		
	Skin hypopigmentation[3]		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail

[2] Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3] BMS-936558 (Nivolumab, MDX-1106) being a member of class of agents involved in the inhibition of "immune checkpoints", may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[4] Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[5] Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

[6] Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving BMS-936558 (Nivolumab, MDX-1106). These complications may occur despite intervening therapy between receiving BMS-936558 (Nivolumab, MDX-1106) and allo-SCT.

[7] Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

Adverse events reported on BMS-936558 (Nivolumab, MDX-1106) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that BMS-936558 (Nivolumab, MDX-1106) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - LEUKOCYTOSIS

CARDIAC DISORDERS - ATRIAL FIBRILLATION; ATRIOVENTRICULAR BLOCK COMPLETE; HEART FAILURE; VENTRICULAR ARRHYTHMIA

EAR AND LABYRINTH DISORDERS - VESTIBULAR DISORDER

EYE DISORDERS - EYE DISORDERS - OTHER (IRIDOCYCLITIS); OPTIC NERVE DISORDER; PERIORBITAL EDEMA

GASTROINTESTINAL DISORDERS - CONSTIPATION; DUODENAL ULCER; FLATULENCE; GASTROINTESTINAL DISORDERS - OTHER (MOUTH SORES); VOMITING

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - CHILLS; EDEMA LIMBS; MALAISE; PAIN

HEPATOBILIARY DISORDERS - BILE DUCT STENOSIS

IMMUNE SYSTEM DISORDERS - ANAPHYLAXIS; IMMUNE SYSTEM DISORDERS - OTHER (AUTOIMMUNE THROMBOTIC MICROANGIOPATHY); IMMUNE SYSTEM DISORDERS - OTHER (LIMBIC ENCEPHALITIS)

INFECTIONS AND INFESTATIONS - BRONCHIAL INFECTION; LUNG INFECTION; SEPSIS; UPPER RESPIRATORY INFECTION

INVESTIGATIONS - BLOOD LACTATE DEHYDROGENASE INCREASED; GGT INCREASED; INVESTIGATIONS - OTHER (PROTEIN TOTAL DECREASED); LYMPHOCYTE COUNT INCREASED; WEIGHT LOSS

METABOLISM AND NUTRITION DISORDERS - DEHYDRATION; HYPERURICEMIA; HYPOALBUMINEMIA; HYPOCALCEMIA; HYPONATREMIA; HYPOPHOSPHATEMIA

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - BACK PAIN; MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER (MUSCULOSKELETAL PAIN); MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER (POLYMYALGIA RHEUMATICA); MYALGIA; PAIN IN EXTREMITY

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER (HISTIOCYTIC NECROTIZING LYMPHADENITIS)

NERVOUS SYSTEM DISORDERS - DIZZINESS; HEADACHE; INTRACRANIAL HEMORRHAGE

PSYCHIATRIC DISORDERS - INSOMNIA

RENAL AND URINARY DISORDERS - HEMATURIA; RENAL AND URINARY DISORDERS - OTHER (TUBULOINTERSTITIAL NEPHRITIS)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - BRONCHOSPASM; COUGH; DYSPNEA; HYPOXIA

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - ALOPECIA; DRY SKIN; HYPERHIDROSIS; PAIN OF SKIN; PHOTOSENSITIVITY; RASH ACNEIFORM; SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER (ROSACEA)

VASCULAR DISORDERS - FLUSHING; HYPERTENSION; HYPOTENSION; VASCULITIS

NOTE: BMS-936558 (Nivolumab, MDX-1106) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Rev. Add17

5.5 Dose Modifications

As of the activation of addendum #16, all toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

5.5.1 Dose Modifications for Ipilimumab

5.5.1.1 Dose and Schedule Modifications for Ipilimumab

There will be no intra-patient dose reductions for ipilimumab. The dose of ipilimumab will either be given or delayed/discontinued. Patients may develop study drug-related toxicities that may require delaying doses or dose discontinuation. Some of these adverse events may be consistent with potentially drug-related immune-mediated phenomena; termed IRAEs. Details of how to dose study medication in the presence of adverse drug reactions that may or may not be IRAEs are addressed below.

Patients will delay or discontinue treatment with ipilimumab if they experience at least one adverse event, specified below, considered by the investigator to be possibly, probably or definitely related to ipilimumab treatment. The following criteria will be used to determine dosing delay, restarting doses, and whether ipilimumab should be permanently discontinued. For an adverse event, the investigator should review the following criteria in a stepwise manner: First, assess the dose delay criteria and decide whether a scheduled dose should be delayed. If a dose is delayed and does not meet the dosing criteria within the protocol allowed 3-day window it may be delayed up to 6 weeks to allow resolution of the event. If the patient is able to receive ipilimumab within this 6 week window and no further toxicity occurs, the patient will receive all planned doses of ipilimumab. Second, determine whether the permanent discontinuation criteria apply to the adverse event in question as well**.**

NOTE: Standard vaccinations may be given with ipilimumab as they pose no known risk of increasing immune reactions. However, their efficacy in conjunction with ipilimumab is not known. Therefore we suggest that routine vaccinations, including seasonal influenza be given at least 2 weeks prior to study treatment if at all possible.

5.5.1.1.1 Criteria to delay one dose of ipilimumab

Missed doses will not be made up. Patient will resume the normal ipilimumab schedule and will receive all remaining doses.

Delay ipilimumab dosing for the following treatment related adverse events:

- Any ≥ Grade 2 non-skin related adverse event (including IRAEs) except for laboratory abnormalities.
- Any ≥ Grade 3 laboratory abnormality, or ≥ Grade 2 liver abnormalities, or hyperbilirubinemia.
- Any ≥ Grade 3 skin-related adverse event (including IRAEs) regardless of causality.

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Rev. 1/15

Rev. Add16

5.5.1.1.2 Criteria to resume ipilimumab treatment

For adverse event(s) that do not meet the ipilimumab permanent discontinuation criteria as noted below, resume ipilimumab dosing at the next scheduled treatment if/when the dose delaying adverse event(s) resolve(s) to ≤ Grade 1 severity or returns to baseline.

- If the adverse event has resolved (to ≤ Grade 1 severity or returns to baseline), restart ipilimumab dosing at the time that the adverse event has resolved.
- If the adverse event has resolved within 6 weeks the dose may be given at the next scheduled timepoint for Ipilimumab. Missed doses will not be made up.

Please note that for each scheduled dose there is a [+/- 3 days] window within which a scheduled dose may still be given if the dose delaying AE(s) has resolved to ≤ grade 1. It is per investigator's discretion if other agents should be delayed and administered with ipilimumab.

For patients with grade 2 diarrhea who meet the criteria for resuming dosing with ipilimumab after resolution to baseline should have a colonoscopy (with or without biopsy) to confirm the resolution of the inflammation before ipilimumab may be resumed.

If patients have not recovered from ipilimumab related adverse events within 6 weeks, discontinue ipilimumab.

5.5.1.1.3 Criteria for permanent discontinuation of ipilimumab for Related Adverse Events

Ipilimumab administration must be permanently discontinued if any of the following Related Adverse Events occur:

- Any ≥ Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to ≤ Grade 1 severity within 2 weeks of starting therapy for this adverse event, OR, requires systemic treatment.
- Any ≥ Grade 3 bronchospasm or other hypersensitivity reaction.
- Any other ≥ Grade 3 non-skin related adverse event with the exception of events listed under “Exceptions to Permanent Discontinuation” (See Section 5.5.1.1.4)
- Any ≥ Grade 4 laboratory abnormalities, except AST, ALT, or Total Bilirubin, for which permanent discontinuing criteria is as follows :
  - 2 or more episodes of ≥ grade 3 AST or ALT 5-20 x ULN.
  - Total Bilirubin > 5 x ULN.

NOTE: An exception to permanent discontinuation of ipilimumab is made for laboratory abnormalities that are rapidly reversible, not life threatening, do not reflect underlying organ system dysfunction, and are not related to ipilimumab, such as transient elevations of uric acid, hypocalcaemia, or hypophosphatemia.

- Any other skin related ≥ Grade 3 adverse event.

NOTE: An exception to permanent discontinuation of ipilimumab is made for skin abnormalities which resolve to baseline after a short course (< 4 weeks) of steroids,

and do not recur for two weeks after discontinuation of steroids.

- Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued dosing.
- Any motor neurologic toxicity ≥ Grade 3 regardless of causality.
- Any ≥ Grade 3 treatment related sensory neurologic toxicity.
- Patients who require high dose steroids, other immune suppressants or anti-TNF drug therapy for the management of immune related adverse events as described in the Toxicity Management Guidelines/Algorithms should have ipilimumab permanently discontinued. Treatment with oral budesonide or moderate dose steroids for grade 2 colitis or grade 2 or lower skin rash or higher dose IV steroids for grade 3 skin rash are criteria for ipilimumab dose delay but not permanent discontinuation.
- Any adverse event which has persisted for more than 6 weeks.
- Any DLT defined under Section 5.1.6 except for a single episode of Grade 3 ALT/AST elevation which resolves to normal baseline within 6 weeks. If patients experience a second episode of Grade 3 ALT/AST elevation, ipilimumab must be permanently discontinued.

5.5.1.1.4 Exceptions to permanent discontinuation of ipilimumab

Ipilimumab administration may be resumed in the following cases:

- Potentially reversible inflammation (< Grade 4), attributable to a local anti-tumor reaction and a potential therapeutic response. This includes inflammatory reactions at sites of tumor resections or in draining lymph nodes, or at sites suspicious for, but not diagnostic of metastasis.

- Hospitalization for ≤ Grade 2 adverse events where the primary reason for hospitalization is to expedite the clinical work-up and management.
- Patients with the following conditions where in the investigator's opinion continuing study drug administration is justified:
  - Ocular toxicity that has responded to topical therapy.
  - Endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy.
  - Skin toxicity which has resolved to baseline within 4 weeks of initiating corticosteroid therapy, and does not recur within 2 weeks of steroid discontinuation.

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NOTE: Ipilimumab may not be restarted while the patient is being treated with systemic corticosteroids except for patients on stable doses of hormone replacement therapy such as hydrocortisone. If patients have not recovered within 6 weeks, ipilimumab must be discontinued.

NOTE: If Ipilimumab is restarted and there are subsequent cumulative or severe toxicities ipilimumab must be discontinued.

5.5.1.1.5 Differentiating the primary attribution of a certain adverse event and implications on holding a dose and permanent discontinuation.

NOTE: An attempt should be made to differentiate the primary attribution of a certain adverse event to ipilimumab and nivolumab versus brentuximab vedotin before a decision on permanent discontinuation is made. In general, most of the AEs related to brentuximab

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vedotin, especially the laboratory abnormalities, are not immunologic in nature, and improve with directed supportive measures. Exceptions to this are pneumonitis which has been reported with all agents, and neuropathy which has principally been reported with brentuximab, and which can be slow to resolve. Ipilimumab and related immune mediated adverse events are often persistent or serious, and require intervention with corticosteroids or other immune suppressants.

Adverse events that are related to the combination regimen and meet the thresholds for dose holding or delay per protocol criteria should lead to holding/delaying both agents until resolution to the protocol required criteria for resumption. Decisions on whether to permanently discontinue one or both agents should be made carefully and independently based on the attributions to one agent or the other. If one agent was discontinued based on a specific related adverse event, the other agent(s) may continue to be dosed if it does not meet the protocol permanent discontinuation criteria for the specific adverse event or if the adverse event is determined to be unlikely related. Both agents may be discontinued at the discretion of the treating physician investigator if felt to be in the best interest of the patient to avoid recurrence or development of serious adverse events.

5.5.1.2 Supportive care considerations for ipilimumab administration

5.5.1.2.1 Treatment of infusion reactions associated with ipilimumab

Since ipilimumab contains only human protein sequences, it is less likely that any allergic reaction will be seen in patients. However, it is possible that infusion of ipilimumab will induce a cytokine release syndrome that could be evidenced by fever, chills, rigors, rash, pruritus, hypotension,

hypertension, bronchospasm, or other symptoms. No prophylactic pre medication will be given unless indicated by previous experience in an individual patient. Reactions should be treated based upon the following recommendations.

- For mild symptoms (e.g., localized cutaneous reactions such as mild pruritus, flushing, rash):
  - Decrease the rate of infusion until recovery from symptoms, remain at bedside and monitor patient.
  - Complete the ipilimumab infusion at the initial planned rate.
  - Diphenhydramine 25-50 mg I.V. may be administered at the discretion of the treating physician and patients may receive additional doses with close monitoring.
  - Premedication with diphenhydramine may be given at the discretion of the investigator for subsequent doses of ipilimumab.
- For moderate symptoms (any symptom not listed above [mild symptoms] or below [severe symptoms] such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic Blood pressure < 80 mmHg):
  - Interrupt ipilimumab.
  - Administer diphenhydramine 50 mg I.V.
  - Monitor patient closely until resolution of symptoms.
  - Corticosteroids may abrogate any beneficial immunologic effect, but may be administered at the discretion of the treating physician.
  - Resume ipilimumab infusion after recovery of symptoms.
  - At the discretion of the treating physician, ipilimumab infusion may be resumed at one half the initial infusion rate, then increased incrementally to the initial infusion rate.

- If symptoms develop after resumption of the infusion, the infusion should be discontinued and no additional ipilimumab should be administered that day.
- The next dose of ipilimumab will be administered at its next scheduled time and may be given with pre-medication (diphenhydramine and acetaminophen) and careful monitoring, following the same treatment guidelines outlined above.
- At the discretion of the treating physician additional oral or IV antihistamine may be administered prior to dosing with ipilimumab.

- For severe symptoms (e.g., any reaction such as bronchospasm, generalized urticaria, systolic blood pressure < 80 mm Hg, or angioedema):
  - Immediately discontinue infusion of ipilimumab, and disconnect infusion tubing from the subject.
  - Consider bronchodilators, epinephrine 1 mg IV or subcutaneously, and/or diphenhydramine 50 mg IV, with solumedrol 100 mg IV, as needed.
  - Patients should be monitored until the investigator is comfortable that the symptoms will not recur.
  - No further ipilimumab will be administered.
  - In case of late-occurring hypersensitivity symptoms (e.g., appearance within one week after treatment of a localized or generalized pruritus), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

5.5.1.2.2 Treatment of Ipilimumab-Related Isolated Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the ipilimumab or to an infectious etiology. If a patient experiences isolated drug fever, for

the next dose, pre-treatment with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion) should be instituted and a repeated antipyretic dose at 6 and 12 hours after ipilimumab infusion, should be administered. The infusion rate will remain unchanged for future doses. If a patient experiences recurrent isolated drug fever following premedication and post dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be decreased to 50% of the previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further ipilimumab.

5.5.1.3 Immune-Related Adverse Events (irAEs): Definition, Monitoring, and Treatment

Blocking CTLA 4 function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis, and hypopituitarism were drug-related, presumptive autoimmune events, now termed irAEs, noted in previous ipilimumab studies.

For the purposes of this study, an irAE is defined as an AE of unknown etiology associated with ipilimumab exposure and consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE an irAE. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Suspected irAEs must be documented on an AE or SAE form.

Patients should be informed of and carefully monitored for evidence of clinically significant systemic irAE (e.g., systemic lupus erythematosus-like diseases) or organ specific irAE (e.g., rash, colitis, uveitis, hepatitis or thyroid disease). If an irAE is noted, appropriate work-up (including biopsy if possible) should be performed, and steroid therapy may be considered if clinically necessary. See following section for suggested work-up and treatment of irAEs.

It is unknown if systemic corticosteroid therapy has an attenuating effect on ipilimumab activity. However, clinical anti-tumor responses have been maintained in patients treated with corticosteroids and discontinued from

ipilimumab. If utilized, corticosteroid therapy should be individualized for each patient.

Corticosteroid replacement therapy is not allowed except for patients who develop endocrinopathies during this study that require corticosteroid replacement therapy (such as hydrocortisone) at stable doses.

5.5.1.4 Suggested evaluation and treatment for Immune Related Adverse Events (irAEs) associated with ipilimumab

NOTE: This information has been summarized from the Ipilimumab Investigator Brochure (IB). Please refer to the current version of the IB for more details on the Suggested Work-up and Treatment for irAEs and Management Algorithms. Although these are suggested guidelines that take into consideration potential variations that may be required based on a specific clinical situation, these guidelines are strongly recommended.

Management algorithms for the early detection and treatment of ipilimumab associated toxicities are provided in Appendices Appendix VIII-Appendix XI.

5.5.1.4.1 Immune-mediated Enterocolitis

Diarrhea (defined as either first watery stool, or increase in frequency 50% above baseline with urgency or nocturnal bowel movement, or bloody stool) should be further evaluated and infectious or alternate etiologies ruled out. Subjects should be advised to inform the investigator if any diarrhea occurs, even if it is mild. An algorithm for managing subjects with diarrhea or suspected colitis is provided in Appendix VIII. It is suggested that prednisone (for oral administration) or solumedrol (for IV administration) be the corticosteroids of choice in the treatment of colitis.

Corticosteroid therapy (e.g., 1 to 2 mg/kg/day of prednisone po or solumedrol I.V. or equivalent) is strongly recommended for ipilimumab related ≥ Grade 3 diarrhea/colitis. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least one month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients.

Subjects with ipilimumab related Grade 2 diarrhea/colitis may be initially treated conservatively, but should be immediately switched to corticosteroids if symptoms persist for more than one week or worsen. For severe or persistent symptoms, prednisone (e.g., 0.5 mg/kg/day) or equivalent may be required to control symptoms. Lower doses of prednisone may be considered for less severe cases of colitis.

If the diarrhea is prolonged or severe or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP or platelet count; or bandemia), it is recommended that sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy of 3 to 5 specimens for standard paraffin block be performed. All subjects with confirmed colitis should also have an ophthalmologic examination, and a slit-lamp exam should be considered at the discretion of the treating physician investigator, to rule out uveitis. Also consider testing for stool calprotectin and stool WBCs. Negative stool testing for calprotectin or WBCs does not rule out autoimmune colitis.

Infrequently, subjects will appear refractory to corticosteroids or will flare following taper of corticosteroids. In these subjects, unless contraindicated (i.e., sepsis and other serious infections, or perforation), a single dose of infliximab at 5 mg/kg may provide benefit. Infliximab 5 mg/kg may be repeated 2 weeks later if clinically indicated.

5.5.1.4.2 Immune-mediated Hepatitis

Liver function tests should always be performed and reviewed prior to administration of all ipilimumab doses. In addition, subjects presenting with right upper quadrant abdominal pain, unexplained nausea, or vomiting should have LFTs performed immediately and reviewed before administering the next dose of study drug. A Hepatotoxicity Management Algorithm is provided in Appendix IX and the current IB.

LFTs ≥ Grade 2 (for subjects with normal baseline LFT) or LFT ≥ 2 times baseline values (for subjects with baseline LFT of Grade 1 or 2) should prompt treating physicians to: (1) increase frequency of monitoring LFTs to at least every 3 days until LFT have stabilized or improved; (2) investigate to rule out non-irAE etiologies; and (3) initiate an autoimmunity evaluation. Disease progression, other malignancies, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and bile ducts should be considered to rule out neoplastic or other non-irAE-related causes for the increased LFTs. An ANA, perinuclear anti-neutrophil cytoplasmic antibody (pANCA), and anti-smooth muscle antibody test should be performed if an autoimmune etiology is considered. Consultation with a hepatologist is appropriate for a suspected liver IRAE and a biopsy should be considered.

For hepatic transaminases > 5 times the upper limit of normal (ULN) or total bilirubin is > 3 times the upper limit of normal: (1) ipilimumab dosing should be held according to the dose modification guidelines, (2) LFTs should be repeated every 24 hours until stabilization or improvement; and (3) therapeutic intervention with high dose corticosteroids should be strongly considered (e.g., prednisone PO or methylprednisolone I.V. 1-2 mg/kg once or twice daily or equivalent). If symptoms or LFT elevations are controlled, the corticosteroid dose should be gradually tapered over a period of at least 1 month. Flare in LFTs during this taper may be treated with an increase in the dose of steroid and a slower taper. Across the clinical development program for ipilimumab, mycophenolate treatment has been administered in patients who have persistent severe hepatitis despite high-dose corticosteroids. The most current experience with immune-related hepatitis has allowed further development of this management algorithm (see flow chart in

Appendix IX and current IB) to include recommendations for treatment.

For hepatic transaminases > 8x the ULN or total bilirubin > 5x the ULN, It is recommended:

a. Admit subject to hospital for evaluation and close monitoring.
b. Stop any further ipilimumab dosing.
c. Start high dose corticosteroids (e.g., 2mg/kg methylprednisolone sodium succinate per day, given IV as a single or divided dose).
d. Check liver laboratory test values (LFTs, T-bilirubin) daily until stable or showing signs of improvement for at least 3 consecutive days.
e. If no decrease in LFTs after 3 days or rebound hepatitis occurs despite treatment with corticosteroids, then add mycophenolate mofetil 1gm BID per institutional guidelines for immunosuppression of liver transplants (supportive treatment as required, including prophylaxis for opportunistic infections per institutional guidelines).
f. If no improvement after 5 to 7 days, consider adding 0.10 to 0.15 mg/kg/day of tacrolimus (trough level 5 20 ng/mL).
g. If target trough level is achieved with tacrolimus but no improvement is observed after 5 to 7 days, consider other immunosuppressant's per institutional guidelines.
h. Continue to check LFTs daily for at least 2 weeks to monitor sustained response to treatment.

5.5.1.4.3 Immune-mediated Pancreatitis

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, may be associated with anti-CTLA-4 monoclonal antibody administration. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include serum amylase and lipase tests.

5.5.1.4.4 Immune-mediated Dermatitis

Monitor patients for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated. A dermatologist should evaluate persistent or severe rash or pruritus. A biopsy should be performed if appropriate and if possible, photos of the rash should also be obtained. Any non-protocol drugs that could contribute to a drug reaction should be stopped if possible pending evaluation.

Patients with low-grade ipilimumab-mediated skin toxicity (Grade 1 or 2) may remain on therapy and could be treated with symptomatic therapy (e.g., antihistamines). Low-grade symptoms persisting for 1 to 2 weeks and relapsing should be treated with topical or moderate dose oral corticosteroid therapy (e.g., prednisone 0.5 mg/kg once daily or equivalent).

High-grade (persistent Grade 3 despite moderate dose oral corticosteroid such as prednisone 1 mg/kg once daily or equivalent, or any Grade 4) symptoms require high-dose IV corticosteroid therapy (e.g., prednisone PO or methylprednisolone I.V. at 1-2 mg/kg once or twice per day or equivalent) to control initial symptoms. A skin biopsy should be performed if appropriate. Once rash or pruritis is controlled, the initiation of corticosteroid taper should be based on clinical judgment; however, the corticosteroid dose should be gradually tapered over a period of at least 1 month.

Patients with any high-grade skin related toxicity (Grade 3 regardless of causality) have to skip ipilimumab and may only continue treatment with ipilimumab if the initial symptoms have improved to ≤ Grade 1, while patients with grade 4 skin toxicities (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations) have to permanently discontinue ipilimumab.

5.5.1.4.5 Immune-mediated Endocrinopathies

Monitor thyroid function tests, other protocol required tests and clinical chemistries at the start of treatment, before each dose, and as clinically indicated based on symptoms. Subjects with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. An endocrinologist should be consulted if an endocrinopathy is suspected. If there are any signs of adrenal crisis such as severe dehydration, hypotension, or shock, intravenous corticosteroids with mineralocorticoid activity (e.g., methylprednisolone) should be initiated immediately. If the patient's symptoms are suggestive of an endocrinopathy but the patient is not in adrenal crisis, endocrine laboratory results should be evaluated before corticosteroid therapy is initiated.

Endocrine work up should include at least Thyroid stimulating hormone and free T4 levels to determine if thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

Radiographic imaging (e.g., MRI) with pituitary cuts should be performed if hypophysitis is suspected. If the pituitary scan and/or endocrine laboratory tests are abnormal and suggestive of pituitary endocrinopathy, a short course of high dose corticosteroids (e.g., dexamethasone 4 mg every 6 hours or equivalent) should be strongly considered in an attempt to treat the presumed pituitary inflammation, but it is currently unknown if this will reverse the pituitary dysfunction.

Abrupt discontinuation of corticosteroids should be avoided due to possible prolonged adrenal suppression. Once symptoms or laboratory abnormalities are controlled, and overall patient improvement is evident, the initiation of steroid taper should be based on clinical judgment; however the corticosteroid dose should be

gradually tapered over a period of at least 1 month. Appropriate hormone replacement therapy should be instituted if an endocrinopathy is documented, and it is possible that subjects may require life-long hormone replacement.

Please see Appendix X and the current IB for the Endocrinopathy Management Algorithm.

5.5.1.4.6 Ocular Manifestations

Ocular inflammation (episcleritis or uveitis), usually in association with colitis, was reported in a few subjects. These conditions responded to topical corticosteroid therapy. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers and retina; visual field testing and an electroretinogram should also be performed. Patients with ipilimumab related uveitis or episcleritis have been treated with topical corticosteroid eye drops. See Section 5.5.1.1.3 for ocular irAEs that may require ipilimumab permanent discontinuation.

5.5.1.4.7 Immune-mediated Neuropathies

Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Permanently discontinue ipilimumab in patients with severe neuropathy (interfering with daily activities) such as Guillain-Barré-like syndrome (GBS). Institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe neuropathies. Withhold ipilimumab dosing in patients with moderate neuropathy (not interfering with daily activities). See the current IB for neuropathy management guidelines.

5.5.1.4.8 Other Immune-mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions were seen in less than 1% of ipilimumab-treated patients

in reported studies to date: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia.

Across the clinical development program for ipilimumab, the following likely immune-mediated adverse reactions were also reported with less than 1% incidence: myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, and autoimmune thyroiditis.

Permanently discontinue ipilimumab for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe immune-mediated adverse reactions.

Administer corticosteroid eye drops to patients who develop uveitis, iritis, or episcleritis. Permanently discontinue ipilimumab for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

5.5.2 Dose Modifications for Brentuximab Vedotin

Intrapatient dose modifications may be done for toxicities related to brentuximab therapy if it is determined by the treating physician that it is in the best interest of the patient for safety reasons taking into consideration the overall clinical status of the subject. A note has to be made of such a modification. After cycle 1, subsequent cycles of therapy may be delayed for up to 3 weeks if additional time is required for the patient to recover from toxicity. Delays of greater than 3 weeks are prohibited and will lead to discontinuation of study participation. For toxicity-related modifications beyond cycle 1, intra-patient dose reduction will be allowed depending on the type and severity of toxicity.

Suggested intra-patient dose modifications of brentuximab vedotin are as follows:

Intrapatient Dose Modification for Brentuximab

Dose Level	Brentuximab vedotin Dose
1	1.8 mg/kg
–1	1.2 mg/kg
–2	0.8 mg/kg

5.5.2.1 Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption. Patients who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption.

5.5.2.2 For toxicities that can be treated or prevented, such as nausea, vomiting, diarrhea and neutropenia, treatment may be resumed at the previous dose once supportive measures have been instituted and toxicity recovers to Grade 2 or less.

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5.5.2.3 The following table summarizes brentuximab vedotin dose modifications

Treatment Modification Guidelines for Brentuximab Vedotin-Related Adverse Events

Rev. Add17

Event	CTCAE.v5.0 Grade	Action to be Taken
Allergic reactions **or** **Acute infusional reactions/cytokine release syndrome**	Grade 1-2	For first reaction: • Hold the infusion and wait 30 to 60 minutes (depending upon the reaction severity). • Treat reactions with diphenhydramine 1 mg/kg (max 50 mg), or follow local institution guidelines. Depending on the reaction severity, dexamethasone 0.2 mg/kg (max 10 mg) IV should be used. • Upon resolution of the symptoms, at the physician's discretion, it may be possible to resume treatment by administering an H2 blocker approximately 30 minutes before restarting the infusion. Acetaminophen can also be considered. Dosing of brentuximab vedotin should be administered at half of the previously administered rate. For subsequent doses: • Utilize diphenhydramine with or without acetaminophen as pre-treatment for all subsequent infusions. • Dosing should be administered over the shortest period that was well tolerated. If Grade 1-2 infusion reactions recur despite the above measures, either during re-challenge or subsequent treatments: • Take the measures outlined above. • With subsequent dosing, add dexamethasone 0.2 mg/kg (max 10mg) IV or equivalent to medications above prior to infusion.

Event	CTCAE.v5.0 Grade	Action to be Taken
	Grade 3	• Stop infusion immediately. • Administer diphenhydramine hydrochloride 1 mg/kg IV (max 50 mg), dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent), bronchodilators for bronchospasms, and other medications as medically indicated. • Once symptoms recover, brentuximab vedotin should not beresumed for that course. • Subsequent courses of brentuximab vedotin may be considered at physicians' discretion, after a discussion and approval by CTEP. • All subsequent infusions should use the following premedications prior to infusion, diphenhydramine hydrochloride 1 mg/kg IV (max 50 mg), dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent). In addition, the infusion should be administered at 50% of the previous infusion rate.
	Grade 4	• Stop infusion immediately. • Administer diphenhydramine hydrochloride 1 mg/kg (max 50 mg) IV, dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent), and other anaphylaxis medications as indicated. • Epinephrine or bronchodilators should be administered as indicated. • Hospital admission for observation may be indicated. • Discontinue brentuximab vedotin.
Anaphylaxis	Any Grade	If anaphylaxis occurs, immediately and permanently discontinue administration of brentuximab vedotin and administer appropriate medical therapy.
Peripheral Neuropathy	Grade 1	Continue at same dose level.
	Grade 2	• Treatment should be delayed until neuropathy improves to Grade 1 or baseline. • Brentuximab vedotin should be reduced by one dose level for subsequent treatments.
	Grade 3	• Treatment should be delayed until neuropathy improves to Grade 1 or baseline. • Brentuximab vedotin should be reduced by one dose level for subsequent treatments. • Patients who develop grade 3 neuropathy after dose reduction of brentuximab vedotin will have to discontinue brentuximab vedotin.
	Grade 4	Discontinue brentuximab vedotin.

Event	CTCAE.v5.0 Grade	Action to be Taken
Pneumonitis	Grade 1	Continue at same dose level.
	Grade 2	If suspected, strongly consider administration of 100 mg of oral or intravenous prednisolone in single daily or two divided doses. The suggested dose for patients who develop pulmonary toxicity is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days. Upon occurrence of pneumonitis, study therapy should be held, and the Study Chair and Research Coordinator should be notified within 48 hours. Rev. Add17 **If this event occurred during the DLT period on the phase I portion of this study, this event must be reported via CTEP-AERS (grade 2 must be reported within 10 calendar days of learning of the event and grades 3-5 must be reported initially via CTEP-AERS within 24 hours, followed by a complete report via CTEP-AERS within 5 calendar days) and requires a discussion with CTEP within 7 days of the study chair being notified of the event, whenever it occurs regardless of the cycle**
	Grade 3-4	If suspected, strongly consider administration of 100 mg of oral or intravenous prednisolone in single daily or two divided doses. The suggested dose for patients who develop pulmonary toxicity is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days. Discontinue brentuximab vedotin. The Study Chair and Research Coordinator should be notified within 48 hours. Rev. Add17 **If this event occurred during the DLT period on the phase 1 portion of this study, this event must be reported via CTEP-AERS (grade 2 must be reported within 10 calendar days of learning of the event and grades 3-5 must be reported initially via CTEP-AERS within 24 hours, followed by a complete report via CTEP-AERS within 5 calendar days) and requires a discussion with CTEP within 7 days of the study chair being notified of the event, whenever it occurs regardless of the cycle**
Progressive Multifocal Leukoencephalopathy (PML)	Any Grade	If PML is suspected, a diagnostic work-up should be performed. The work-up may include, but is not limited to the following: • Neurologic examinations and neurology consultation, as warranted. • Brain MRI. Features suggestive of PML include presence of unifocal or multifocal lesions, mainly of the white matter, which are typically non-enhancing and do not have mass effect. • PCR analysis. JCV DNA, detectable in CSF or in a brain biopsy, is suggestive of PML. Brentuximab vedotin dosing should be held if PML is suspected. If PML is confirmed, brentuximab vedotin should be permanently discontinued.
Lymphopenia	Grade 1-4	Continue at same dose level
Neutropenia	Grade 1-2	Continue at same dose level

Event	CTCAE.v5.0 Grade	Action to be Taken
	Grade 3-4	• Reinstitute growth factor support (GCSF) for treatment of neutropenia until appropriate recovery to ANC ≥1,000/mm^3. • Patients should receive the same dose in the next treatment with myeloid growth factor support. • If Grade 3-4 neutropenia recurs after myeloid growth factor is added, then the patient should be given a dose reduction of brentuximab vedotin for subsequent cycles • Patients who have Grade 3-4 neutropenia after the addition of myeloid growth factor and dose reduction must be removed from protocol therapy. • If two sequential doses of brentuximab vedotin are held due to unresolved grade 4 toxicity, discontinue treatment with brentuximab vedotin.
Thrombocytopenia	Grade 1-2	Continue at same dose level.
	Grade 3-4	• Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then continue on protocol therapy but should resume at one dose reduction. • Patients who experience Grade 3-4 thrombocytopenia after dose reduction must be removed from protocol therapy.
Non-hematologic events (not including electrolyte abnormalities)	Grade 1-2	Continue at same dose level.
	Grade 3-4	• Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then continue on protocol therapy but should resume at one dose reduction. • If non-hematological Grade 3-4 toxicity recurs after one dose reduction, the patient must be removed from protocol therapy.
Electrolyte abnormalities	Grade 1-4	• Continue at same dose level, provided electrolyte toxicity is not medically consequential and has been readily corrected. • If electrolyte abnormality is medically consequential, refer to guidelines above for non-hematologic events. Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption but should receive appropriate medical therapy.

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5.5.3 Dose Modifications for Nivolumab (Arms D, E, F, G, H, I, X, Y, K, L only)

ALL OTHER EVENTS	**Management/Next Dose for Nivolumab and combination Nivolimab/ipililmumab**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1 OR baseline(exceptions as noted below)
Grade 3	Off protocol therapy (exceptions as noted below)
Grade 4	Off protocol therapy (exceptions as noted below)
Recommended management: As clinically indicated	

- Any grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment should go off protocol treatment

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should go off protocol treatment.
- Any grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed independently from underlying organ pathology with electrolyte replacement, hormone replacement, insulin or that does not require treatment does not require discontinuation.

Skin Rash and Oral Lesions	**Management/Next Dose for Nivolumab**
Grade 1	No change in dose *
Grade 2	Hold* until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at same level at investigator discretion
Grade 4	Off protocol therapy
*Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, TEN, and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphagoid. Pruritus may occur with or without skin rash and should be treated symptomatically if there is no associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering.	
Recommended management: AE management guidelines	

Liver Function AST, ALT, Bilirubin	**Management/Next Dose for Nivolumab**
Grade 1	No change in dose.
Grade 2	Hold until ≤ Grade 1 or baseline. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at same level at investigator discretion
Grade 4	Off protocol therapy
Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate LFT changes and early treatment are recommended. LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis.	
Recommended management: see Hepatic AE management algorithm	

Diarrhea/ Colitis	**Management/Next Dose for Nivolumab**
Grade 1	No change in dose
Grade 2	Hold until ≤ 1. No change in dose
Grade 3	Off protocol therapy.
Grade 4	Off protocol therapy
See GI AE Algorithm for management of symptomatic colitis.	

Diarrhea/ Colitis	**Management/Next Dose for Nivolumab**
Patients with grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. Patients who require steroids: see Section 5.5.1.1.3 and Appendix VIII. Please evaluate pituitary function prior to starting steroids if possible without compromising acute care. Evaluation for all patients for additional causes includes *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.	
Recommended management: see GI AE management Algorithm	

Pancreatitis Amylapse/Lipase	**Management/Next Dose for Nivolumab**
Grade 1	No change in dose.
Grade 2	Hold until baseline. Resume at same dose level if asymptomatic
Grade 3	Hold until baseline. Resume at same dose level if asymptomatic. Patients who develop symptomatic pancreatitis or DM should be taken off treatment
Grade 4	Hold until baseline. Resume at same dose level if asymptomatic. Patients who develop symptomatic pancreatitis or DM should be taken off treatment
Patients may develop symptomatic and radiologic evidence of pancreatitis as well as DM and DKA. Lipase elevation may occur during the period of steroid withdrawal and with other immune mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated. For treatment management of symptomatic pancreatitis please follow the Hepatic Adverse Event Management Algorithm	

Pneumonitis	**Management/Next Dose for Nivolumab**
Grade 1	Hold dose pending evaluation and resolution to baseline including baseline pO2. Resume no change in dose after pulmonary and/or ID consultation excludes lymphocytic pneumonitis.
Grade 2	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off study if steroids are required. ^
Grade 3	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off study if steroids are required
Grade 4	Off protocol therapy
Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine for all patients.	
Recommended management: See Pulmonary Adverse Event Management Algorithm	

Other GI N-V	**Management/Next Dose for Nivolumab**
Grade 1	No change in dose.
Grade 2	Hold pending evaluation for gastritis duodenitis and other immune adverse events or other causes. Resume at same dose level after resolution to ≤ Grade 1.
Grade 3	Hold pending evaluation until ≤ Grade 1. Resume at same dose level. If symptoms do not resolve within 7 days with symptomatic treatment patients should go off protocol therapy
Grade 4	Off protocol therapy
Patients with grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.	

Fatigue	**Management/Next Dose for Nivolumab**
Grade 1	No change in dose.
Grade 2	No change in dose
Grade 3	Hold until ≤ Grade 2. Resume at same dose level
Grade 4	Off protocol therapy
Fatigue is the most common adverse event associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation	

Neurologic events (Excluding peripheral neuropathy)	**Management/Next Dose for Nivolumab**
Grade 1	Hold dose pending evaluation and observation. (#) Resume with no change in dose when resolved to baseline.
Grade 2	Hold dose pending evaluation and observation. # Hold until ≤ Grade 1. Off protocol therapy if treatment with steroids is required. Resume at same dose level for peripheral isolated n. VII (Bell's palsy)^
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, myasthenia gravis should be off study.	
Recommended management: See Neurologic Adverse Event Management Algorithm	

Endocrine Hypophysitis Adrenal Insufficiency	**Management/Next Dose for Nivolumab**
Grade 1	Asymptomatic TSH elevation * Hold pending evaluation, endocrine consult
Grade 2	Hold until patients are on a stable replacement hormone regimen. If treated with steroids patients must be stable off steroids for two weeks. Resume at same dose level.
Grade 3	Off study treatment.
Grade 4	Off protocol therapy
Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered grade 3 events. Isolated thyroid or testosterone deficiency may be treated as grade 2 if there are no other associated deficiencies and adrenal function is monitored. Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. *Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement.	
Recommended management: See Endocrine Management Algorithm	

Renal	**Management/Next Dose for Nivolumab and Nivo/Ipi combination**
≤ Grade 1	Evaluate and continue at same dose level if the toxicity is not progressive.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off treatment

Infusion reaction	**Management/Next Dose for Nivolumab and Nivo/Ipi combination**
≤ Grade 1	Evaluate and continue at same dose level if the toxicity is not progressive.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off treatment

Fever	**Management/Next Dose for Nivolumab and Nivo/Ipi combination**
≤ Grade 1	Evaluate and continue at same dose level
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off treatment
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever	
See Section 5.6 infusion reactions	

Cardiac*	**Management/Next Dose for Nivolumab + Ipilimumab Cardiac Toxicities**
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation
Grade ≥ 2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Consult algorithm for more details. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥ 2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone Add ATG or tacrolimus if no improvement. Off treatment.
* *Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ** *Patients with evidence of myositis without myocarditis may be treated according as "other event"* **NOTE:** The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

- Drug will be held for grade 2 cardiac dysfunction pending evaluation
- Drug will be permanently discontinued for grade 3 or 4 cardiac dysfunction and grade 2 events that do not recover to baseline or that reoccur
- Treatment with steroids as clinically indicated

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For patients taking nivolumab/ ipilimumab combination who experience grade 2 or grade 3 events requiring permanent discontinuiation of treatment during the induction phase see Section 5.1.6

If treatment is delayed >6 weeks for an adverse event the patient must be permanently discontinued from study therapy.

Treatment delay is acceptable for up to 8 weeks if the patient is on a steroid taper and has discontinued steroids with symptoms ≤ Grade 1. For all other delays no more than 6 weeks.

Patients requiring high dose steroid treatment for autoimmune or inflammatory events should go off study treatment except for a short course of tapering steroids for infusion reaction, skin rash or endocrine events. See Section 5.5.1.1.4.

Patients with grade 3 thyroiditis and skin rash may continue therapy as for grade 2 events with resolution and stable replacement treatment.

Patients with thyroiditis or hypopituitarism who are stable as above may be restarted with replacement hormones including thyroid hormone and physiologic doses of corticosteroids.

Please note that grading for hypophysitis with symptoms of headache, visual or neurologic changes or radiologic evidence of pituitary enlargement and other CNS events such as aseptic meningitis or encephalitis should be considered grade 3 events.

Any patients who require additional immune suppressive treatment beyond steroids should go off study treatment

Patients requiring > two dose delays for the same event should go off protocol therapy.

Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, ACTH, TSH and T4 must be obtained to document baseline.

Please note that in some cases the treatment algorithms recommend steroids if symptoms do not resolve in 7 days. However, this recommendation is not meant to delay steroid treatment at any time it is clinically indicated.

Patients may be dose-delayed for evaluation and restarted depending on results.

Any patient started on corticosteroids initially who is determined to not require steroid treatment for an autoimmune adverse event may

resume therapy after a 2 week observation period without further symptoms at the discretion of the PI or investigator.

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5.6 Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, urticaria, angioedema, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

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All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as medically appropriate:

Remain at bedside and monitor subject until recovery from symptoms

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Infusion rate may be slowed or interrupted and restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely.

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations, slowing infusion rate as above.

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For Grade 2 symptoms: Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for $\leq$ 24 hours).

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, re administer diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and (acetaminophen) (or paracetamol) 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction),

Grade 3 symptoms: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]).

Grade 4 symptoms: (life threatening; pressor or ventilatory support indicated).

Nivolumab will be permanently discontinued

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the investigator is comfortable that the symptoms will not recur.

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids). Additional treatment prior to next dose as per guidelines above.

Please note that late occurring events including isolated fever and fatigue may represent the presentation of systemic inflammation. Please evaluate accordingly.

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5.7 Criteria for resuming treatment with nivolumab or ipilimumab

If treatment is held for immune toxicity, restarting therapy applies only to grade 2 events and some grade 3 events (skin rash and thyroiditis).

For non-autoimmune or non-inflammatory events patients may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue
- Evaluation to exclude any additional immune mediated events endocrine, GI, and liver / pancreas function as clinically indicated must be made prior to restarting.
- Non-drug-related toxicity including hepatic, pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.

If the criteria to resume treatment are met, the patient should restart treatment no sooner than the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol the treatment should resume at the earliest convenient point that is within the six week delay period.

If treatment is delayed for > 6 weeks, (> 8 weeks for patients on a steroid taper), the patient must be permanently discontinued from study therapy, except as specified in Section 5.5.

If there is clear toxicity attributed to one of the agents that requires discontinuation of that agent patient may continue other study agents.

For patients treated with corticosteroids:

Patients requiring high dose steroid treatment for autoimmune or inflammatory events should go off study treatment except for a short course of tapering steroids for infusion reaction, skin rash or endocrine events. See Section 5.5.1.1.4.

Patients with grade 3 thyroiditis and skin rash may continue therapy as for grade 2 events with resolution and stable replacement treatment.

Patients with thyroiditis or hypopituitarism who are stable as above may be restarted with replacement hormones including thyroid hormone and physiologic doses of corticosteroids.

Please note that grading for hypophysitis with symptoms of headache, visual or neurologic changes or radiologic evidence of pituitary enlargement and other CNS events such as aseptic meningitis or encephalitis should be considered grade 3 events.

Any patients who require additional immune suppressive treatment beyond steroids should go off study treatment

Patients requiring > two dose delays for the same event should go off protocol therapy.

Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, ACTH, TSH and T4 must be obtained to document baseline.

Please note that in some cases the treatment algorithms recommend steroids if symptoms do not resolve in 7 days. However, this recommendation is not meant to delay steroid treatment at any time it is clinically indicated.

Patients may be dose-delayed for evaluation and restarted depending on results.

Any patient started on corticosteroids initially who is determined to not require steroid treatment for an autoimmune adverse event may resume therapy after a 2 week observation period without further symptoms at the discretion of the PI or investigator. Please note that in some cases the treatment algorithms recommend steroids if symptoms do not resolve in 7 days. However, this recommendation is not meant to delay steroid treatment at any time it is clinically indicated.

5.8 Supportive Care

5.8.1 All supportive measures consistent with optimal patient care will be given throughout the study.

5.8.2 See Section 5.5.1.2 and Appendices Appendix VIII-Appendix XI for supportive care considerations for ipilimumab administration.

5.8.3 See Section 5.5.2 for supportive care considerations for brentuximab vedotin administration.

5.8.4 See Section 5.5.3 for supportive care considerations for nivolumab administration.

5.8.5 Patients requiring chemotherapy or radiation therapy during the study will be taken off study treatment. Any exceptions must be discussed with the study chair.

5.8.6 Additional Prohibited and Restricted Therapies During the Study.

5.8.6.1 Prohibited Therapies

Patients in this study may not use vaccines for the treatment of cancer for up to one month pre and post dosing with ipilimumab and nivolumab. Concomitant systemic or local anti-cancer medications including biologics, or radiation therapy treatments are prohibited in this study while receiving ipilimumab, nivolumab, and brentuximab.

- Any non-study anti-cancer agent (investigational or non-investigational)
- Any other investigational agents
- Any other CTLA-4 inhibitors or agonists
- CD137 agonists, PD-1 inhibitors
- Immunosuppressive agents, unless indicated to manage study therapy induced irAEs
- Chronic systemic corticosteroids, unless indicated to manage study therapy induced irAEs or chronic GVHD at a stable dose prior to study entry
- Rev. Add16 Though vaccines are not prohibited on study (during both phase I and II components), they must be given at least 6 weeks after cycle 1 and not within 7 days of treatment. It is suggested that routine vaccinations, including seasonal influenza, be given at least 2 weeks prior to study treatment. Any non-oncology vaccine therapies used for the prevention of infectious diseases outside these parameters should be discussed with the study chair prior to administration.

Rev. 9/16, Add16 5.9 Duration of Therapy – Phase I and II

Patients will receive protocol therapy unless:

5.9.1 Hodgkin lymphoma disease progression by protocol criteria: in which case patients will be removed from study treatment. They will, however, continue to be followed for survival. In addition, data on salvage patterns post recurrence will be collected.

5.9.2 Patients will be discontinued from treatment in the event of unacceptable toxicity (see protocol therapy discontinuation criteria in Section 5.5), clinical deterioration as demonstrated by a significant decrease in performance status, pregnancy, change in medical condition or noncompliance with the study protocol that in the opinion of the investigator, necessitates removal of patient from treatment.

5.9.3 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment

should be discontinued. In this event, submit forms according to the schedule in the E4412 Forms Completion Guidelines.

5.9.4 Patient withdraws consent.

5.9.5 Non-protocol therapies are administered.

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5.10 Duration of Follow-up – Phase I and II

For this protocol, all Phase I patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 3 years from the date of registration.

All Phase II patients, including those who discontinue protocol therapy early, will be followed for 10 years for response until progression, even if non-protocol therapy is initiated, and for survival for 10 years from the date of registration. Patients will be followed for 10 years from the date the last patient is enrolled.

All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

Rev. Add16 Response will be evaluated both locally and centrally. The baseline PET study to confirm eligibility, PET after 4 cycles and after 12 cycles of therapy will be used for central measurement of response.

Lymphoma Response Criteria

NOTE: For phase I patients, these criteria are based upon the criteria from the Revised Response Criteria for Malignant Lymphoma, (Cheson et al.), Journal of Clinical Oncology, 2007, Vol. 25:579-586.

Rev. Add16 **NOTE:** For phase II patients, response will be assessed by Central Review according to the Lugano response criteria (Cheson et al, Journal of Clinical Oncology, 2014 Vol. 32:3059-68.). Additional refinements to this criteria will also be used for response assessment (Cheson et al, Blood, 2016, Vol. 128:2489-96.). Response will be evaluated both locally and centrally. The baseline, PET study that documents relapse, after 4 cycles, and PET after 10 cycles of therapy will be used for central measurement of response.

Rev. Add16 The criteria use the following categories of response: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Indeterminate Response (IR), Relapse and Progression (PD). In the case of stable disease, follow-up assessments must have met the SD criteria at least once after study entry at a minimum interval of six weeks.

The following guidelines are to be used for establishing tumor measurements at baseline and for subsequent comparison:

- The six largest dominant nodes or extranodal masses must be identified at baseline.
- If there are 6 or fewer nodes and extranodal masses, all must be listed as dominant
- If there are more than 6 involved nodes or extranodal masses, the 6 largest dominant nodes or extranodal masses should be selected according to the following features: a) they should be clearly measurable in at least two perpendicular measurements; b) they should be from as disparate regions of the body as possible; and c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- Measurements for all dominant nodes and extranodal masses will be reported at baseline. Measurements on non-dominant nodes are not required.
- The lymph nodes or extranodal masses selected for measurement should be measured in two perpendicular diameters, one of which is the longest perpendicular diameter. The lymph nodes should be measured in centimeters to the nearest one tenth of a centimeter (e.g.,2.0 cm, 2.1cm, 2.2 cm, etc.)
- The two measured diameters of each lymph node site or extranodal mass should be multiplied giving a product for each nodal site or extranodal mass. The product of each nodal site should be added, yielding the sum of products of the diameters (SPD). The SPD will be used in determining the definition of response for those who have less than a complete response.

Deauville Scores should be assessed for patients in Arms K and L using the following values:

- 1, no FDG uptake above background;

- 2, FDG uptake ≤ mediastinum;
- 3, FDG uptake > mediastinum but ≤ liver;
- 4, FDG uptake moderately > liver;
- 5, FDG uptake markedly higher than liver and/or new lesions;
- X, new areas of uptake unlikely to be related to lymphoma

*Score 5 will be applied when the SUV_{max} of the lesion is 2x to 3x greater than the SUV_{max} of the liver.

6.1 Complete Response

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6.1.1 Phase I Criteria

Complete disappearance of all detectable clinical evidence of disease, and disease-related symptoms if present prior to therapy.

6.1.1.1 In patients with a typically FDG-avid lymphoma with no pre-treatment PET scan, or for lymphomas for which the PET scan was positive prior to therapy: a post-treatment residual mass of any size is permitted as long as it is PET-negative.

6.1.1.2 For variably FDG-avid lymphomas without a pretreatment PET scan, or if a pretreatment PET scan was negative: all lymph nodes and extranodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm prior to therapy). Previously involved nodes that were 1.1-1.5 cm in their long axis and > 1.0 cm in their short axis prior to treatment must have decreased to ≤ 1 cm in their short axis after treatment.

6.1.1.3 The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination, and nodules related to lymphoma should disappear. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size and involvement. For instance, a spleen considered normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma, but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes.

NOTE: Complete Remission/unconfirmed (CRu): Using the above definition for CR and that below for PR eliminates the category of CRu.

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6.1.2 Phase II Criteria

Please use the phase I CR criteria above in addition to the following:

6.1.2.1 Deauville Score of 1, 2, or 3 with or without a residual mass or nodal lesion; residual masses are allowed if not FDG avid.

6.1.2.2 In Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with

chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.

6.1.2.3 No new lesions.

No evidence of FDG avid focal lesion in marrow unless as noted in Section 6.1.2.2.

6.2 Partial Response (PR)

6.2.1 Phase I Criteria

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The designation of PR requires all of the following:

6.2.1.1 The designation of PR requires all of the following:A ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or extranodal masses. These nodes or masses should be selected according to the following: (a) they should be clearly measurable in at least 2 perpendicular dimensions; if possible, they should be from disparate regions of the body; (b) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

6.2.1.2 No increase in the size of other nodes, liver or spleen.

6.2.1.3 No new sites of disease.

6.2.1.4 For a typically FDG-avid lymphoma with no pretreatment PET scan or one that was PET-positive prior to therapy, the post-treatment PET should be positive at any previously involved sites.

6.2.1.5 For variably FDG-avid lymphomas/FDG-avidity unknown, without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT scan criteria should be used.

6.2.1.6 Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvementwill be considered partial responders.

6.2.1.7 When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

6.2.2 Phase II Criteria

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Please use the phase I PR criteria above in addition to the following:

6.2.2.1 Deauville Score of 4 or 5 with reduced uptake compared to baseline and residual mass(es) of any size.

6.2.2.2 No new lesions.

6.2.2.3 Residual marrow uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with a BM biopsy.

6.3 Stable Disease (SD)

Failing to attain the criteria needed for a PR or CR, but not fulfilling those for progressive disease (see below).

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6.3.1 Phase I Criteria:

6.3.1.1 Typically FGD-avid lymphomas: The PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

6.3.1.2 For variably FDG-avid lymphomas/FDG-avidity unknown: For patients without a pretreatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

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6.3.2 Phase II Criteria:

Please use the phase I SD criteria above in addition to the following:

6.3.2.1 Deauville score 4 or 5 with no significant change in FDG uptake from baseline.

6.3.2.2 No new lesions.

6.3.2.3 No change in marrow uptake from baseline.

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6.4 Progression (PD) and Relapse

6.4.1 Phase I Criteria:

6.4.1.1 For determination of relapsed and progressive disease, lymph nodes should be considered abnormal if the long axis is more than 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if the short axis is more than 1 cm. Lymph nodes ≤ 1 x ≤ 1 cm will not be considered as abnormal for relapse or progressive disease.

6.4.1.2 Treatment decisions in patients with presumed refractory, relapsed or progressive disease should not be made solely on the basis of a single PET scan without histologic confirmation.

6.4.1.3 Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size.

6.4.1.4 Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior

history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

6.4.1.5 At least a 50% increase from nadir in the SPD of any previously involved nodes or extranodal masses, or in a single involved node or extranodal mass, or the size of other lesions (e.g. splenic or hepatic nodules). To be considered progressive disease, a lymph node or extranodal mass with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 cm x 1.5 cm or more than 1.5 cm in the long axis.

6.4.1.6 At least a 50% increase in the longest diameter of any single previously identified node or extranodal mass more than 1 cm in its short axis.

6.4.1.7 Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

6.4.1.8 Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these response criteria, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

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6.4.2 Phase II Criteria:

Please use the phase I PD criteria above in addition to the following:

6.4.2.1 New FDG-avid foci consistent with lymphoma.

6.4.2.2 New or recurrent FDG-avid foci in the bone marrow.

Patients who achieve PD [in a conventional way] will additionally be assessed using the LYRIC criteria. Please see below for information on Indeterminate Response (IR). If a patient is assessed as having IR and then “true” PD at a subsequent time point, the IR assessment should subsequently be corrected to PD for reporting purposes to the date of the prior designation of IR.

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6.5 Indeterminate Response Evaluation and Endpoints

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Ipilimumab and nivolumab are expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some patients may experience tumor flare with objective volume increase of tumor lesions or other disease parameters (based on study indication, ie, hematologic malignancies) within 12 weeks following the start of dosing. Such patients may not have had sufficient time to develop the required immune activation or, in some patients, tumor volume or other disease parameter increases may represent

infiltration of lymphocytes into the original tumor or blood. For this reason, we will additionally use the Lyric Criterion outlined below to evaluate responses considered to be Indeterminate Response (IR) (95). A patient should be considered to have IR if they 1 or more of the following:

6.5.1 IR(1): Increase in overall tumor burden (as assessed by sum of the product of the diameters [SPD]) of ≥50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration.

6.5.2 IR(2): Appearance of new lesions or growth of one or more existing lesion(s) ≥ 50% at any time during treatment; occurring in the context of lack of overall progression (< 50% increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during the treatment.

6.5.3 IR(3): Increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size or number.

Follow up of IR:

In patients categorized as having any of the above types of IR, it is mandatory to obtain a repeat imaging after an additional 12 weeks (or earlier if clinically indicated). At that time, response should be re-evaluated and the patient should be considered to have true PD if the SPD of target lesions have increased further, with the considerations below:

- In the case of IR(1) the comparison should be between the first IR(1) and the current SPD, with an increase of > 10% constituting PD. In addition, there should be an increase of > 5 mm (in either dimension) of at least one lesion for lesions < 2 cm, and 10 mm for lesions > 2 cm, to be consistent with the Lugano classification (3)(Table 2). The 10% threshold is empiric but designed to account for variability in measurement (37), especially when taken along with the minimum increase. If the target SPD increase is < 10%, the response would still be categorized as IR(1), and the patient could continue treatment until a subsequent scan shows either true PD (> 10% increase from first IR(1) time point and an increase of > 5 mm in either dimension of at least one lesion) or response (> 50% decrease from baseline). In this situation, it is reasonable to repeat imaging in 4-8 weeks of the original IR(1) time point to ensure absence of significant further increase.
- In the case of IR(2), the new or growing lesion(s) (unless biopsy proven to be benign) should be added to the target lesion(s), up to a total of no more than 6 total lesions. If the SPD of the newly defined set of target lesions has increase ≥ 50% from their **nadir** value (which may precede the IR time point), the patient should be considered to have PD.
- In the case of IR(3), since inflammatory responses may result in an increase in the standardized uptake value of a lesion, the patient will not be considered to have PD unless there is evidence of PD by an increase in lesion size or the development of new lesions, as noted above.

Please reference updates to the Lugano response criteria for further information on determination and follow up of IR.

6.6 Duration of Response

This is measured from the documented beginning of response (CR or PR) to the time of relapse. This is measured in responders.

6.7 Survival

Survival is defined as the date of study entry to the date of death.

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6.8 Progression-Free Survival

Progression-free Survival (PFS) is defined as the time from entry onto study until lymphoma progression or death from any cause. PFS is often considered the preferable endpoint in lymphoma clinical trials, especially those involving incurable histologic subtypes (e.g., follicular and low grade, mantle cell lymphoma). PFS reflects tumor growth and, therefore, occurs prior to the endpoint of overall survival. In addition, PFS is not confounded by the administration of subsequent therapy. Whether a prolongation of PFS represents direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit ratio of the therapy under investigation. Unlike survival, the precise date of progression is generally unknown. It may be defined as the first date of documentation of a new lesion or enlargement of a previous lesion, or the date of the scheduled clinic visit immediately after radiologic assessment has been completed. Where there is missing information, censoring of the data may be defined as the last date at which progression free status was adequately documented.

7. Study Parameters

7.1 Phase I – Therapeutic Parameters

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1. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done ≤ 4 weeks prior to registration.
2. Prestudy CBC (with differential and platelet count) should be done ≤ 2 weeks prior to registration.
3. All required prestudy chemistries, as outlined in Section 3.1, should be done ≤ 2 weeks prior to registration – unless specifically required on Day 1 as per protocol.
4. See Section 7.1.1 below regarding biologic sample submissions.
5. All assessments and treatment cycles are +/- 3 days.

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	Prior to Registration	C1 Day 1[s]	C1 Day 8	C1 Day 15	C2 Day 1 [s]	C3 Day 1 [s]	C4 Day 1 [s]	C5-16 Day 1 [s,t,u]		C17 and beyond: Day 1 [u,v]	End of Study [p]
Tests and Observations[b]											
History and Physical Exam, Vital Signs, SO2, Weight, BSA, Performance Status	X	X	X	X	X	X	X	X	X	X	X
Height	X										
Pulmonary Assessment [r]	X										
Adverse Event Assessment [l]	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Peripheral Neuropathy Assessment	X	X	X	X	X	X	X	X	X	X	X
Ophthalmologic Examination [k]	X										X
Laboratory Studies [b]											
CBC with Differential [a,d] Platelets	X	X	X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Test [g]	X	X			X	X	X		X	X	
ESR and LDH	X	X			X	X	X	X	X	X	X
Chemistry Labs [e]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis [f]	See footnote f										
HIV, HBV, HCV [h]	X										
Immunologic Labs [i]	X										X
Endocrine Labs [j]	X								X		X

	Prior to Registration	C1 Day 1[s]	C1 Day 8	C1 Day 15	C2 Day 1 [s]	C3 Day 1 [s]	C4 Day 1 [s]	C5-16 Day 1 [s,t,u]		C17 and beyond: Day 1 [u,v]	End of Study [p]
EKG [q]	X										
Staging Studies [m]											
CT Scan or FDG-PET/CT scan [n]	X						X [m] (before cycle 4)		X [m]	X [m]	X [m]

a CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct required for protocol therapy must be done < 24 hours prior to the treatment cycle.

Rev. Add16 b. All Study procedures, blood samples collected for pretreatment laboratory tests may be collected and analyzed no more than 3 days prior to dosing. Chemistry results must be reviewed and confirm that subject's liver function tests and other safety labs still meet inclusion criteria prior to administration of ipilimumab dose. Baseline pregnancy exam must be performed within 24 hours of beginning ipilimumab dosing and determined to be negative. They should be seen and evaluated more often if clinically indicated for the management of toxicities, at the discretion of the treating physician investigator. Hormonal studies and immunologic labs are required for monitoring at the specified time points and as clinically indicated. The results of these tests (hormonal studies and immunologic labs) are not required for dosing unless there are clinical indications and/or associated adverse events as described under Section 5.5.1 Dose and Schedule Modifications for Ipilimumab.

Rev. 8/14 c. For first infusion only, vital signs to be collected prior to dosing, every 15 minutes (-/+ 5 minutes) during dosing and 30 minutes (-/+ 10 minutes) after treatment completion until vital signs normalize or return to baseline. For vital signs that are normal/return to baseline at the 30 minutes (-/+10 minutes) assessment, **no additional vitals are required.** For subsequent infusions, vital signs should be collected prior to dosing and every 30 minutes (-/+ 10 minutes) during dosing. After treatment completion: Patients who have never had a documented infusion reaction, post-dosing vital signs may be obtained at 30 minutes post infusion.

d. Hematology labs to include hemoglobin, hematocrit, red blood cell count, white blood cell count, platelets (direct platelet count), as well as total and differential CBC counts. These labs must be done and reviewed before ipilimumab infusion. These labs are required to be done throughout follow-up regardless if the patient goes off treatment early for anything other than recurrence. Once recurrence occurs, these labs are no longer required to be completed.

e. Chemistry laboratory analysis includes albumin, amylase, lipase, urea or BUN, creatinine, ALT, AST, LDH, serum alkaline phosphatase, direct and total bilirubin, glucose, total protein, sodium, potassium, chloride, HCO3 (CO2; venous blood), calcium, phosphorous. In follow up (after completion of ipilimumab treatment), amylase and lipase will be done only if clinically indicated. These labs must be done and reviewed before ipilimumab infusion. These labs are required to be done throughout follow-up regardless if the patient goes off treatment early for anything other than recurrence. Once recurrence occurs, these labs are no longer required to be completed.

f. Urinalysis will be done as clinically indicated. Urinalysis tests to include gross examination including specific gravity, protein, glucose and blood. A microscopic evaluation will also be performed, as clinically indicated, to include WBC/HPF, RBC/HPF and any additional findings.

Rev. 5/17
Rev. Add16 g. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 2 weeks prior to enrollment. Serum or urine pregnancy test must be done within 24 hours prior to each dose of ipilimumab, and every 2 cycles with nivolumab for beyond cycle 16.

h. At screening, testing should be performed for HIV antibody, hepatitis C antibody, and HBs antigen utilizing local standard informed consent procedures prior to this laboratory collection. These tests could be repeated later during the course of the study if clinically indicated.

i. The following immunologic analysis labs are to be done at baseline within 28 days prior to starting Ipilimumab Dosing (Arms A, B, C, Z and G, H, I, X) and at HL relapse if treatment is discontinued due to relapse. If HL relapse occurs before any time point, no additional testing needs to be done after the relapse time point: C-reactive protein, Antinuclear antibody (ANA) Screen, Thyroid Stimulating Immunoglobulin (TSI), Antithyroglobulin antibody (ATGAB), Antithyroperoxidase Antibody (ATPOAB), Anticardiolipin Antibody (TOTAL). These labs must be completed even if the patient goes off treatment early for any reason other than progression.

Rev. Add16 j. Endocrine labs: To be done at the indicated visits and when clinically indicated. These include TSH, free T4, morning ACTH, morning cortisol. For Men: testosterone. For WOCBP: prolactin, LH, FSH, and estradiol that will be done only if a WOCBP is experiencing amenorrhea while on protocol treatment. These tests should be completed pre-treatment and per investigator discretion.

k. Ophthalmologic examination will be done at baseline only if clinically indicated. Ophthalmological examination is strongly recommended to be done at 6 and 18 months (± 4 weeks) after start of treatment, especially in patients who experience diarrhea or colitis, preferably performed by an ophthalmologist. If recurrence occurs before these time points, the ophthalmological examination should still be done if clinically indicated. It should also be performed at other time points if clinically indicated.

l. All adverse events must be collected whether they occur on treatment or non-treatment weeks and must be submitted utilizing the corresponding E4412 Adverse Event Forms, covering all time periods specified on the forms.

m. Scans will be performed at baseline within 28 days of registration, before cycle 4, and thereafter every 3 months. During follow-up scans can be SOC (so that there are no radiology charges).

n. It is critical that all FDG PET/CT or CT scans be performed in an identical way to the baseline scan with the same scanner, same scan direction, and consistent arm pointing. The interval between FDG injection and initiation of emission scanning should be the same or similar to the baseline scan. Patients suspected of tumor flare may continue scans per standard protocol schedule, but during this time should have no deterioration in PS and not require any additional immediate treatment. If progression is documented at time of the second scan, patient must come off study.

o. Follow up assessments will be every 3 months (+/- 2 weeks) if patient is < 2 years from study entry and every 6 months (+/- 4 weeks) if patient is 2-3 years from study entry. However, patients with ongoing toxicities should be seen more often as clinically indicated. Patients who develop recurrent HL will be followed for survival and for information on salvage patterns. The schedule of clinical follow up for these patients will be at the discretion of the treating physicians and according to established Standard of Care. Adverse Events Assessment on the study will continue for all patients until 30 days after the last study drug administration.

p. End of Study Assessment will be done within 6 weeks (+/- 1 week) of the last dose of study treatment. If still in remission, end of study scan must be completed within 6 weeks (+/- 1 week) of the last dose of study treatment UNLESS patient received a scan within 4 weeks of the last dose of study treatment. In this case, the next scan would be completed no sooner than 12 weeks from their previous scan. After end of study assessment, scans for patients in follow-up can be SOC.

Rev. Add16 q. EKG to be obtained within 30 days prior to starting treatment. EKG and echo-cardiograms should also be conducted as clinically indicated for any patients with a history of CHF or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs. For patients with evidence of CHF, MI, cardiomyopathy, or myositis, further cardiac evaluation, lab tests and cardiology consultations, including EKG, CPK, troponin, and ECHO cardiogram, should be conducted as clinically indicated.

r. Pulmonary fuction testing to be performed within 28 days prior to registration. Repeat testing if patients develop any signs or symptoms suggestive of pulmonary dysfunction.

s. Brentuximab vedotin and Ipilimumab to be given together on Day 1 of cycles 1-4, 8, 12, and 16 (Arms A, B, C, and Z).

t. Brentuximab vedotin and Nivolumab to be given together on Day 1 of cycles 1-16. Cycle Length: 21 days (Arms D, E, F, and Y).

u. Brentuximab vedotin and Nivolumab to be given together on Day 1 of cycles 1-16 q21 days. If Brentuximab vedotin is discontinued early subsequent Nivolumab cycles will be q14 days.

Rev. 5/17 v. Ipilimumab q6 weeks (42 days) for Arms A, B, C, Z and q12 weeks (84 days) for Arms G, H, I, and X.

7.1.1 Phase I – Biological Sample Submissions

Rev. 9/15

Specimens are to be submitted as outlined in Section 11.

Rev. 9/16, Add16

All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS).

	Prior to Start of Treatment	Prior to Cycle Two (2)[4]	Time of First Restaging PET/CT [+/- 3 days]	After Completion of Therapy/Off Treatment	Submit to:
MANDATORY for Central Diagnostic Review					
Tumor Tissue Biopsy[15]	X				CBPF
Submit from patients who answer *"Yes"* to *"I agree to participate in the laboratory research studies that are being done as part of this clinical trial."*					
Peripheral Blood [green top tubes, (6) 10mL tubes, 60mL	X	X[4]	X	X	Mayo Clinic Lymphoma Laboratory
Submit from patients who answer *"Yes"* to "*I agree biopsies may be done to obtain research specimens*" at institutions that have met the guidelines outlined in Section 11.					
Rev. 1/15, Rev. Add16 Tumor Tissue Biopsy[1,2,5]		X[3]		X[6]	CBPF

1. Representative tumor tissue from the initial diagnostic, and relapse confirmatory biopsies and the research biopsies and related pathology reports and Sample Tracking System shipping manifest form are to be submitted within one (1) month following registration or collection as outlined in Section 11.
2. Biopsy research rates and reimbursement guidelines are outlined in Section 11.6. Prior to recruiting patients to the research biopsy portion, the following conditions must be met:
   a. The research rates of $3,750 for CT guided core needle biopsies and $3,100 for US guided core needle biopsies are deemed acceptable by the IRB or central research office.
   b. The research rate is reported to the institution's financial office and an account established in the principal investigator's name.
3. Collect on day 1 of cycle 2 prior to treatment.
4. Collect +/- 7 days prior to cycle 2.
5. Rev. Add16 The tumor tissue biopsies will also be used for the optional laboratory research studies outlined in Section 12 for those patients who have consented to participate.
6. If patient comes off treatment.

Rev. Add16

7.2 Phase II – Therapeutic Parameters

1. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done ≤ 4 weeks prior to registration.
2. Prestudy CBC (with differential and platelet count) should be done ≤ 2 weeks prior toregistration.
3. All required prestudy chemistries, as outlined in Section 3.2, should be done ≤ 2 weeks prior to registration – unless specifically required on Day 1 as per protocol.
4. See Section 7.1.1 below regarding biologic sample submissions.
5. All assessments, scans, and treatment cycles are +/- 3 days.

	Prior to Registration	C1 Day 1	C1 Day 8	C1 Day 15	C2 Day 1	C3 Day 1	C4 Day 1	C5-16 Day 1[f,k]	C17 and beyond: Day 1 [f,k]	End of Study [p,o]
Tests and Observations[b]										
History and Physical Exam, Vital Signs, SO2, Weight, BSA, Performance Status [c]	X	X	X	X	X	X	X	X	X	X
Height	X									
Pulmonary Assessment [i]	X									
Adverse Event Assessment [l]	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Peripheral Neuropathy Assessment	X	X	X	X	X	X	X	X	X	X
Laboratory Studies [b]										
CBC with Differential [a,d] Platelets	X	X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Test [g]	X	X			X	X	X	X	X	
ESR and LDH	X	X			X	X	X		X	X
Chemistry Labs [e]	X	X	X	X	X	X	X	X	X	X
HIV, HBV, HCV [h]		X								
Endocrine Labs [j]		X						X		X
EKG [q]	X									

	Prior to Registration	C1 Day 1	C1 Day 8	C1 Day 15	C2 Day 1	C3 Day 1	C4 Day 1	C5-16 Day 1[f,k]	C17 and beyond: Day 1 [f,k]	End of Study [p,o]
Staging Studies[m]										
CT Scan or FDG-PET/CT scan [n]	X							X[m]	X[m]	X[m]

a CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct required for protocol therapy must be done < 24 hours prior to the treatment cycle.

b. All Study procedures, blood samples collected for pretreatment laboratory tests may be collected and analyzed no more than 3 days prior to dosing. Chemistry results must be reviewed and confirm that subject's liver function tests and other safety labs still meet inclusion criteria prior to administration of ipilimumab dose. Baseline pregnancy exam must be performed within 24 hours of beginning ipilimumab dosing and determined to be negative. They should be seen and evaluated more often if clinically indicated for the management of toxicities, at the discretion of the treating physician investigator. Hormonal studies and immunologic labs are required for monitoring at the specified time points and as clinically indicated. The results of these tests (hormonal studies and immunologic labs) are not required for dosing unless there are clinical indications and/or associated adverse events as described under Section 5.5.1 Dose and Schedule Modifications for Ipilimumab.

Rev. Add20 c. For first infusion only, vital signs to be collected prior to dosing, every 15 minutes (-/+ 5 minutes) during dosing and 30 minutes (-/+ 10 minutes) after treatment completion until vital signs normalize or return to baseline. For vital signs that are normal/return to baseline at the 30 minutes (-/+10 minutes) assessment, **no additional vitals are required.** For subsequent infusions, vital signs should be collected prior to dosing and every 30 minutes (-/+ 10 minutes) during dosing. After treatment completion: patients who have never had a documented infusion reaction, post-dosing vital signs may be obtained at 30 minutes post infusion. Additionally, SO2 should be monitored as a vital sign during each visit. If the patient has had previously documented infusion reactions, vitals should be SOC as clinically indicated after infusion.

d. Hematology labs to include hemoglobin, hematocrit, red blood cell count, white blood cell count, platelets (direct platelet count), as well as total and differential CBC counts. These labs must be done and reviewed before ipilimumab infusion. These labs are required to be done throughout follow-up regardless if the patient goes off treatment early for anything other than recurrence. Once recurrence occurs, these labs are no longer required to be completed.

Rev. Add19 e. Chemistry laboratory analysis includes albumin, amylase, lipase, urea or BUN, creatinine, ALT, AST, serum alkaline phosphatase, direct and total bilirubin, glucose, total protein, sodium, potassium, chloride, HCO3 (CO2; venous blood), calcium, phosphorous. In follow up (after completion of ipilimumab treatment), amylase and lipase will be done only if clinically indicated. These labs must be done and reviewed before ipilimumab infusion. These labs are required to be done throughout follow-up regardless if the patient goes off treatment early for anything other than recurrence. Once recurrence occurs, these labs are no longer required to be completed.

Rev. Add20 f. Brentuximab vedotin and Nivolumab to be given together on Day 1 of cycles 1-16 q21 days. If Brentuximab vedotin is discontinued early subsequent Nivolumab cycles will be q21 days.

Rev. Add20 g. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) at pre-registration and within 24 hours prior to cycle 1 . For patients receiving ipilimumab on Arm L, serum or urine pregnancy test must be done within 24 hours of day 1 C1-4;, then within 24 hours of ipilumab dose for C5 and beyond until ipilimumab is discontinued. After ipilimumab discontinuation, serum or urine pregnancy test must be done within 24 hours of nivolumab dose every 2 cycles during nivolumab treatment. For patients on Arm K, serum or urine pregnancy test must be dune within 24 hours of nivolumab dose every 2 cycles.

h. At screening, testing should be performed for HIV antibody, hepatitis C antibody, and HBs antigen to meet eligibility requirements in Section 3.2.18 if clinically indicated utilizing local standard informed consent procedures prior to this laboratory collection. These tests could be repeated later during the course of the study if clinically indicated. If concern for viral reactivation, testing may be reported as clinically indicated.

Rev. Add20 i. Pulmonary fuction testing to be performed within 28 days prior to registration, as immunotherapy and brentuximab vedotin may cause pneumonitis. Repeat testing as clinically indicated if patients develop any signs or symptoms suggestive of pulmonary dysfunction. Pulse oximetry testing (SAO2) should follow this same pulmonary function testing schedule as clinically indicated

Rev. Add20 j. Endocrine labs: To be done at the indicated visits and when clinically indicated. These include TSH, free T4 (if TSH is abnormal and/or as clinically indicated), morning ACTH. These tests should be completed prior to first dose of study treatment on cycle 1 day 1 and subsequently at the principal investigator's discretion. If these laboratory studies are not covered by a patient's insurance with the exception of baseline thyroid studies, they can be waived at the judgement of the treating investigator as clinically indicated.

Rev. Add20 k. Ipilimumab q12 weeks (84 days) for Arm L.

Rev. Add20 l. All adverse events must be collected whether they occur on treatment or non-treatment weeks and must be submitted utilizing the corresponding E4412 Adverse Event Forms, covering all time periods specified on the forms.

Rev. Add20 m. Before and during treatment: Scans will be performed at baseline within 28 days of registration, then q3 months during year 1 of treatment and q4 months in year 2 of treatment; for patients who achieve a CR scan on an interim analysis in year 1 of treatment, the scanning interval can be lengthened to q4 months in year 1.If patients come off study before comingtwo years, their end of treatment scan should happen after their final cycle of therapy. During follow-up, scans should be completed q6 months during the first year [of follow-up] and annually during the second year [of follow-up]; scans may also be completed as clinically indicated. Please refer to NCCN guidelines.

n. PET scans will be obtained for central review after cycles 4 and 12 for both study arms and PET scans that were obtained prior to study registration at relapse will be collected for central response evaluation. It is critical that all FDG PET/CT or CT scans be performed in an identical way to the baseline scan with the same scanner, same scan direction, and consistent arm pointing. The interval between FDG injection and initiation of emission scanning should be the same or similar to the baseline scan. Patients suspected of tumor flare may continue scans per standard protocol schedule, but during this time should have no deterioration in PS and not require any additional immediate treatment. If progression is documented at time of the second scan, patient must come off study.

Rev. Add20 o. Follow up assessments will be every 3 months (+/- 2 weeks) if patient is < 1 years from study entry, every 4 months (+/- 2 weeks) if patient is 1 year from study entry, and every 6 months (+/- 4 weeks) if patient is 2-3 years from study entry. However, patients with ongoing toxicities should be seen more often as clinically indicated. Patients who develop recurrent HL will be followed for survival and for information on salvage patterns. The schedule of clinical follow up for these patients will be at the discretion of the treating physicians as clinically indicated and according to established Standard of Care. Adverse Events Assessment on the study will continue for all patients until 30 days after the last study drug administration.

p. End of Study Assessment will be done within 6 weeks (+/- 1 week) of the last dose of study treatment. If still in remission, end of study scan must be completed within 6 weeks (+/- 1 week) of the last dose of study treatment UNLESS patient received a scan within 4 weeks of the last
Rev. Add20 dose of study treatment. In this case, the next scan would be completed no sooner than 12 weeks from their previous scan. After end of study assessment, scans for patients in follow-up should be as clinically indicatedEnd of Study Assessment will be done within 6 weeks (+/- 1 week) of the last dose of study treatment. If still in remission, end of study scan must be completed within 6 weeks (+/- 1 week) of the last dose of study treatment UNLESS patient received a scan within 4 weeks of the last dose of study treatment. In this case, the next scan would be completed no sooner than 12 weeks from their previous scan. After end of study assessment, scans for patients in follow-up should be as clinically indicated.

Rev. Add20 q. EKG monitoring should occur at the baseline assessment and as clinically indicated. If myocarditis is suspected, please refer to AppendixXIX.

7.2.1 Phase II - Biological Sample Submissions

Specimens are to be submitted as outlined in Section 11.

All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS).

	Prior to Start of Treatment	Prior to Cycle Two (2)[4]	Time of First Restaging PET/CT [+/- 5 days]	Every Three [3] Months During Treatment	Grade Three [3] or Greater Toxicity	After Completion of Therapy/Off Treatment	Submit to:
MANDATORY for Central Diagnostic Review							
Tumor Tissue Biopsy[1,5]	X						CBPF
Rev. Add19, Add20 — Submit from patients who answer *"Yes"* to *"I agree that my samples and related health information may be used for the laboratory studies."*							
Peripheral Blood [green top tubes, (6) 10mL tubes, 60mL[12]	X	X[4]	X	X[7]	X[8]	X	Mayo Clinic Lymphoma Laboratory
Submit from patients who answer "*Yes"* to "*I agree to provide additional samples for research."*							
Rev. Add19, Add20 — Stool Specimen[10, 11]	X		X	mon 9		X	NYU
Submit from patients who answer *"Yes"* to "*I agree biopsies may be done to obtain research samples*" at institutions that have met the guidelines outlined in Section 11.							
Tumor Tissue Biopsy[1,2,5]		X[3]	X[9]			X[6]	CBPF

1. Representative tumor tissue and related pathology reports and Sample Tracking Systemshipping manifest form are to be submitted within one (1) month following randomization or collection as outlined in Section 11.
2. Biopsy research rates and reimbursement guidelines are outlined in Section 11.6. Prior to recruiting patients to the research biopsy portion, the following conditions must be met:
   a. The research rates of $3,750 for CT guided core needle biopsies and $3,100 for US guidedcore needle biopsies are deemed acceptable by the IRB or central research office.
   b. The research rate is reported to the institution's financial office and an account established in the principal investigator's name.
3. Collect on day 1 of cycle 2 prior to treatment.
4. Collect +/- 7 days prior to cycle 2.
5. The tumor tissue biopsies will also be used for the optional laboratory research studies outlined in Section 12 for those patients who have consented to participate.
6. If patient comes off treatment.
7. Every three (3) months during treatment for up to two (2) years.
8. Collect 30mL of peripheral blood any time patients are presenting with grade 3 or greater toxicity.
9. For patients with PR, SD, or PD.

Rev. Add19 10. Stool specimens should be collected and submitted at the following timepoints: 1) prior to start of treatment, 2) time of first PET/CT scan, 3) 9 months after first registration, and 7) at time of discontinuation of protocol treatment.

11. Kits are being provided for the collection and shipment of stool specimens. See Appendix XX for instructions. Kit orders will on average be delivered within three (3) business days from the time the order is placed.

12. Kits are being provided for the collection and shipment of the peripheral blood specimens. See Section 11.3.1.

Rev. 9/15

8. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

Availability

Drug Ordering: Bristol-Myers Squibb is supplying ipilimumab **and nivolumab**, through the Division of Cancer Treatment and Diagnosis, NCI, for this protocol. Maintenance of NCI drug accountability records is required. Ipilimumab (NSC 732442 and IND# 133111) **and nivolumab (NSC 748726)** may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that provided drugs be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained – see general information).

The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

NOTE: Under no circumstances can commercially supplied ipilimumab or nivolumab be used or substituted for the NCI-supplied ipilimumab or nivolumab.

Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators must return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at (240) 276-6575.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at (240) 276-6575.

8.1 Ipilimumab

In this study, the investigational product is ipilimumab.

8.1.1 Drug Name

Ipilimumab (NSC 732442)

8.1.2 Other Names

Anti-CTLA-4 monoclonal antibody, MDX-010 (MDX-CTLA4, Transfectoma-derived)

8.1.3 Classification

Human monoclonal antibody, IgG1 subclass

M.W.: 147, 991 Daltons

Ipilimumab has two manufacturing processes- ongoing trials have been using substances manufactured using Process B. This trial, E4412, uses ipilimumab that is manufactured by Process C. The Process C has been developed using a higher producing sub-clone of the current Master Cell Bank, and modified cell culture and purification steps.

8.1.4 Mode of Action

Ipilimumab is specific for the CTLA4 antigen expressed on a subset of activated T cells. CTLA4 interaction with the B7 molecule, one of its ligands expressed on professional antigen presenting cells, can down-regulate T-cell response. Ipilimumab is thought to act by blocking the interaction of CTLA4 with the B7 ligand, resulting in a blockade of the inhibitory effect of T-cell activation. The CTLA4/B7 creates the interaction.

8.1.5 Storage and Stability

Ipilimumab is available in 5 mg/mL single-use vials (40 mL). The sterile solution in the vial is clear and colorless. Ipilimumab is administered via intravenous infusion only. Ipilimumab must be stored in a secure area according to local regulations. The investigator must ensure that it is stored at a temperature $\geq$ 2°C and $\leq$ 8°C.

Ipilimumab is given undiluted or further diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP to a concentration between 1 mg/mL and 4 mg/mL. Undiluted or diluted ipilimumab solution is stable in a polyvinyl chloride (PVC), non- PVC/non DEHP (di-(2-ethylhexul) phthalate) IV bag or glass container up to 24 hours refrigerated at (2°C to 8°C) or at room temperature/ room light.

Shelf-life surveillance of the intact vials is ongoing.

CAUTION: Ipilimumab does not contain antibacterial preservatives. Use prepared IV solution immediately. Discard partially used vials.

Each vial is a Type I flint glass vial with gray butyl stoppers and sealed with aluminum seals.

Component	200 mg/ vial[a]
Ipilimumab	213 mg
Sodium Chloride, USP	249 mg
TRIS-hydrochloride	134.3 mg
Diethylenetriamine pentacetic acid	1.67 mg
Mannitol, USP	426 mg
Polysorbate 80 (plant-derived)	4.69 mg
Sodium Hydroxide	QS to pH 7
Hydrochloric acid	QS to pH 7
Water for Injection	QS: 10.7 mL
Nitrogen[b]	Processing agent

[a] Includes 2.6 mL overfill.

[b] Nitrogen is used to transfer the bulk solution through the pre-filled and sterilizing filters into the aseptic area.

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Rev. 9/16
Rev. 5/17
Rev. Add16

8.1.6 Dose Specifics

Phase I Dose Escalation: Arms A, B, Z only

Ipilimumab 0.3 mg/kg (Arm Z), 1 mg/kg (Arm A), or 3 mg/kg (Arm B) administered by IV infusion day 1 every 21 days for 4 doses, and then every 3 months for a total of 7 doses, until local recurrence or distant progression, unacceptable toxicity or withdrawal of consent.

Phase I Expansion Cohort: Arm C only

Ipilimumab at determined Maximum Tolerated Dose, administered by IV infusion every 21 days for 4 doses, and then every 3 months for a total of 7 doses, until local recurrence or distant progression, unacceptable toxicity or withdrawal of consent. As of January 2015, the dose escalation part of the study has been completed, and the Maximum Tolerated Dose has been determined to be 3 mg/kg. This will be the dose for the expansion cohort.

Phase I Dose Escalation: Arms G, H, X only

Ipilimumab 1mg/kg (Arm G), 1 mg/kg (Arm H), or 1 mg/kg (Arm I) administered by IV infusion day 1 every 12 weeks through nivolumab treatment.

Phase I Expansion Cohort: Arm I only

Ipilimumab will be given at 1 mg/kg administered by IV infusion every 12 weeks through nivolumab treatment.

Phase II Cohort: Arm L only

Ipilimumab will be given at 1 mg/kg administered by IV infusion every 12 weeks through nivolumab treatment.

8.1.6.1 Ipilimumab Dose Calculations

The total dose must be calculated using the most recent subject weight (obtained within 3 days of the dosing visit, and prior to the infusion). Dose delays are allowed as per the dosing criteria described later in this section. Infusions

should be given over 90 minutes (not bolus or IV push) for Arms A, B, C, and Z. Infusions should be given over 30 minutes (not bolus of IV push) for Arms G, H, I, X, and L.

Rev. Add19

Calculate Total Dose as follows:

Patient body weight in kg x [dose mg/kg] = total dose in mg

Calculate Total Infusion Volume as follows:

Total dose in mg ÷ 5 mg/mL = infusion volume in mL

Calculate Rate of Infusion as follows:

Infusion volume in mL ÷ infusion time minutes = rate of infusion in mL/min.

For example, a patient on Arm G (ipilimumab 1 mg/kg) weighing 114 kg (250 lb) would be administered 114 mg of ipilimumab (114 kg x1 mg/kg = 114 mg) with an infusion volume of 22.8 mL (114 mg ÷ 5 mg/mL = 22.8 mL) at a rate of approximately 0.76 mL/min (22.8 mL ÷ 30 minutes) in 30 minutes.

8.1.7 Preparation

The supplies needed for Ipilimumab preparation and administration include calibrated syringes and infusion containers. Ipilimumab is to be administered as an intravenous infusion using an in-line filter (pore size of 0.2 micrometer to 1.2 micrometer) and a volumetric pump. Doses for Arms A, B, C, and will be infused over 90 minutes. Doses for arms G, H, I, L, and X will be infused over 30 minutes. All infusions will be followed with a 10-mL normal saline flush.

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- As ipilimumab is stored at refrigerated temperatures (2-8ºC), allow the appropriate number of vials of ipilimumab to stand at room temperature for approximately five minutes.
- Aseptically withdraw the required volume of ipilimumab solution into a syringe. Insert the needle at an angle into the ipilimumab vial by placing the needle – bevel side down – against the glass, with the tip touching the neck of the vial. The initial solution concentration is 5 mg/mL. [Note: A sufficient excess of ipilimumab is incorporated into each vial to account for withdrawal losses].
- Ensure that the ipilimumab solution is clear colorless, essentially free from particulate matter on visual inspection. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall, etc.
- Inject ipilimumab solution withdrawn into an appropriate size evacuated infusion bag to produce a final infusion volume that has been calculated from the weight of the patient. For example, if preparing a 3mg/kg treatment for a 65 kg patient you will use 2 vials of the 200 mg vial size (or 195 mg).

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- For smaller drug volumes, add the ipilimumab to a convenient volume of 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP to maintain a concentration between 1 mg/mL and 4 mg/mL.

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- Mix by GENTLY inverting several times. DO NOT shake.
- Visually inspect the final solution. If the initial diluted solution or final dilution for infusion is not clear or contents appear to contain precipitate, the solution should be discarded.
- Do not draw into each vial more than once. Any partial vials should be safely discarded and should not be stored for reuse.

8.1.8 Route of Administration

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Ipilimumab is administered as an IV infusion only. Infusions should be given over 90 minutes (not bolus or IV push) for Arms A, B, C, and Z. Infusions should be given over 30 minutes (not bolus or IV push) for Arms G, H, I, L, and X. Ipilimumab should be administered under the supervision of a physician experienced in the use of intravenous (IV) agents.

8.1.9 Incompatibilities

No compatability information is available.

8.1.10 Availability

Bristol-Myers-Squibb is supplying ipilimumab, through the Division of Cancer Treatment and Diagnosis, NCI, for this protocol.

8.1.11 Nursing/Patient Implications

Monitor patients for immune-related adverse events, e.g., rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis and hypothyroidism. If you suspect toxicity, refer to the protocol guidelines for ruling out other causes.

Ipilimumab may be excreted in milk or cross the placenta; therefore, nursing women and women with known or suspected pregnancy should not take ipilumumab.

Closely monitor patients who are on narcotics during the treatment with ipilumumab. Narcotics may mask GI signs and symptoms such as diarrhea or abdominal pain, which are relevant complications of a bowel perforation. Minor diarrhea can be a potential sign of colitis and require immediate attention.

8.1.12 Handling and Disposal

As with all injectable drugs, care should be taken when handling and preparing ipilimumab. Whenever possible, ipilimumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique. Latex gloves are required. If ipilimumab concentrate or solution comes in contact with skin or mucosa, immediately and thoroughly wash with soap and water. After final drug reconciliation, unused ipilimumab solution should be disposed at the site following procedures for the disposal of anticancer drugs.

8.1.13 Ipilimumab Destruction

Partial vials can be destroyed on site per institution policy. Intact vials of expired drug, recalled, or unwanted investigational agent must be returned to PMB, using the NCI Return Agent Form available at http://ctep.cancer.gov or calling the PMB at 240-276-6575. **Under no**

circumstances may investigational agent be destroyed without receiving permission from PMB.

8.2 Brentuximab Vedotin

8.2.1 Other Names

SGN-35

8.2.2 Classification

Monoclonal Antibody

8.2.3 Mode of Action

Brentuximab vedotin is a CD30-directed antibody drug conjugate that consists of three components: the chimeric IgG1 antibody cAC10 which is specific for human CD30; a microtubule disrupting agent, monomethylauristatin E (MMAE); and a protease-cleavable linker that covalently attaches MMAE to cAC10.

The anticancer activity of brentuximab vedotin is due to the binding of antibody drug conjugate to CD30 expressing cells, followed by internalization of the antibody conjugate-CD30 complex, and the release of MMAE via proteolytic cleavage. The binding of MMAE to tubulin disrupts the microtubule network within the cell, resulting in cell cycle arrest, apoptosis, and cell death.

8.2.4 Storage and Stability

Brentuximab vedotin is supplied as 50-mg single-use lyophilized-powder vial. The sterile powder in the vial is white to off-white. Brentuximab vedotin is administered via intravenous infusion only. Vials of brentuximab vedotin must be stored at a temperature of 2 to 8 °C, and protected from light.

Brentuximab vedotin 50-mg lyophilized powder is reconstituted using 10.5mL of Sterile Water of Injection, USP, to produce a reconstituted concentration of 5 mg/mL. The reconstituted solution should be further diluted immediately into 100 mL 0.9% Sodium Chloride injection, 5%Dextrose Injection or Lactated Ringer's Injection to a concentration of 0.4mg/mL to 1.8 mg/mL, or stored at 2 to 8 °C, and should be used within 24 hours of reconstitution.

8.2.5 Dose Specifics

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Phase I Dose Escalation: Arms A, B, and Z

Brentuximab 1.8 mg/kg IV every 21 days starting Cycle 1 Day 1 for a total of 16 doses or until local recurrence or distant progression, unacceptable toxicity or withdrawal of consent.

Phase I Expansion Cohort: Arm C

Brentuximab 1.8 mg/kg IV every 21 days starting Cycle 1 Day 1 for a total of 16 doses or until local recurrence or distant progression, unacceptable toxicity or withdrawal of consent.

NOTE: Brentuximab Vedotin Dose Calculations: use baseline weight at study entry for calculating the dose of brentuximab vedotin. Doses will be adjusted for patients who experience a ≥ 10% change in weight from baseline. For patients weighing greater than 100 kg, bretuximab

vedotin dose will be calculated based on 100 kg. The dose will be rounded to the nearest whole number of milligrams.

Phase I Dose Escalation: Arms D, E, Y, G, H, and X

Brentuximab vedotin 1.2 mg/kg (Arms D, G, Y, and X) or 1.8 mg/kg (Arms E and H) administered by IV every 21 days starting Cycle 1 Day 1 for a total of 16 doses or until unacceptable toxicity or withdrawal of consent.

Phase I Expansion Cohort: Arms F and I

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Brentuximab vedotin 1.8 mg/kg IV every 21 days starting Cycle 1 Day 1 for a total of 16 doses or until local recurrence or distant progression, unacceptable toxicity or withdrawal of consent. As of July 2016, the dose escalation for the brentuximab vedotin and nivolumab combination therapy (Arms D and E) has been completed, and the Maximum Tolerated Dose has been determined to be 1.8 mg/kg. This will be the dose for the brentuximab vedotin and nivolumab expansion cohort (Arm F).

NOTE: Brentuximab Vedotin Dose Calculations: use baseline weight at study entry for calculating the dose of brentuximab vedotin. Doses will be adjusted for patients who experience a ≥ 10% change in weight from baseline. For patients weighing greater than 100 kg, bretuximab vedotin dose will be calculated based on 100 kg. The dose will be rounded to the nearest whole number of milligrams.

Phase II: Arm K and L

Brentuximab 1.8 mg/kg IV every 21 days starting Cycle 1 Day 1 for a total of 16 doses or until local recurrence or distant progression, unacceptable toxicity or withdrawal of consent.

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NOTE: Brentuximab Vedotin Dose Calculations: use baseline weight at study entry for calculating the dose of brentuximab vedotin. Doses will be adjusted for patients who experience a ≥ 10% change in weight from baseline. For patients weighing greater than 100 kg, bretuximab vedotin dose will be calculated based on 100 kg. The dose will be rounded to the nearest whole number of milligrams.

8.2.6 Preparation

- Use appropriate aseptic technique and procedures for handling anticancer drugs when preparing this medication.
- All waste should be treated as hazardous disposal.
- Calculate the dose and number of vials required (Note: the dose for patients > 100 kg should be calculated using 100 kg).
- Reconstitute each 50 mg vial with 10.5 mL of Sterile Water for injection to produce a single-use solution of 5 mg/mL brentuximab vedotin.
- Do not inject Sterile Water for injection directly at the cake or powder, direct the diluent toward wall of vial.

- Gently swirl the vial.
- The reconstituted solution should be clear to slightly opalescent, colorless, and free of visible particulates.
- Immediately add the reconstituted solution to 100 mL 0.9% Sodium Chloride injection, 5% Dextrose injection, or Lactated Ringer's injection.
- Gently invert the bag to mix the solution. Do not shake.
- Final concentration should be 0.4 mg/mL to 1.8 mg/mL brentuximab vedotin.
- Solution can be stored at 2 to 8 oC up to 24 hours if not use immediately. Do not freeze.
- Do not mix Brentuximab vedotin with, administer as an infusion with, other medical products.

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8.2.7 Route of Administration

Brentuximab vedotin is administered as an IV Infusion only over 30 minutes for Arms A, B, C, and Z and over 90 minutes for Arms D, E, F, G, H, I, X, Y, K, and L.

8.2.8 Incompatibilities

Data on compatibility are not available

8.2.9 Availability

Brenduximab Vedotin is available commercially.

8.2.10 Nursing/Patient Implications

- Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness,
- Monitor patients for infusion-related reactions, including anaphylaxis.
- Monitor patients for new onset of signs and symptoms of central nervous system abnormalities.
- It is unknown whether brentuximab vedotin is excreted in human milk. There is a potential for serious adverse effects to a nursing infant if brentuximab vedotin gets excreted into milk. Consideration should be given on whether to discontinue nursing or discontinue Brentuximab vedotin.

8.2.11 References

1. Package Insert. Adcetris (brentuximab vedotin). 2012; Seattle Genetics Inc. Bothell, WA.

8.3 Nivolumab (NSC 748726)

8.3.1 Amino Acid Sequence:

4 polypeptide chains, which include 2 identical heavy chains with 440 amino acids and 2 identical light chains.

8.3.2 Other Names:

BMS-936558, MDX1106

8.3.3 Classification:

Anti-PD-1MAb

8.3.4 M.W.:

146,221 daltons

8.3.5 Mode of Action:

Nivolumab targets the programmed death–1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor. PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Nivolumab inhibits the binding of PD-1 to PD-L1 and PD-L2. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

8.3.6 Description:

Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate, sodium chloride, mannitol, diethylenetriamine pentacetic acid (pentetic acid) and polysorbate 80 (Tween® 80), and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5).

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8.3.7 How Supplied:

Nivolumab is supplied by Bristol-Myers Squibb and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as 100 mg vials (10 mg/mL) with a 0.7 mL overfill. It is supplied in 10 mL type I flint glass vials, with fluoropolymer film-laminated rubber stoppers and aluminum seals.

8.3.8 Dose Specifics

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The dosing calculations should be based on the actual body weight. If the patient's weight on the day of dosing differs by > 10% from the weight used to calculate the original dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.

Phase I Dose Escalation:

Nivolumab 3 mg/kg IV every 21 days in combination therapy and then every 14 days for up to 46 doses, or until local recurrence or distant progression, unacceptable toxicity or withdrawal of consent.

Phase I Expansion Cohort:

Nivolumab 3 mg/kg IV every 21 days in combination therapy and then every 14 days for up to 46 doses, or until local recurrence or distant progression, unacceptable toxicity or withdrawal of consent.

Phase II: Arms K and L

Nivolumab 360mg IV every 21 days for up to 34 doses, or until local recurrence or distant progression, unacceptable toxicity or withdrawal of consent.

8.3.9 Preparation:

Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose. When the dose is based on patient weight (i.e., mg/kg), nivolumab injection can be infused undiluted or diluted to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 360 mg, flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion set, and glass bottles.

8.3.10 Storage:

Vials of Nivolumab injection must be stored at 2°-8°C (36°-46°F) and protected from light, freezing, and shaking. The unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours.

If a storage temperature excursion is identified, promptly return Nivolumab to 2°C-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

8.3.11 Stability:

Shelf-life surveillance of the intact vials is ongoing.

The administration of undiluted and diluted solutions of Nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 8 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

CAUTION: The single-use dosage form contains no antibacterial preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 8 hours after initial entry.

8.3.12 Route of Administration:

Nivolumab is administered as an intravenous infusion over 30 miuntes. Do not administer as an IV push or bolus injection.

8.3.13 Method of Administration:

Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding polyethersulfone membrane in-line filter.

8.3.14 Potential Drug Interactions:

The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

8.3.15 Availability

Nivolumab is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Nivolumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI.

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9. Statistical Considerations

9.1 Phase I

9.1.1 Study Design and Objectives

Three phase I arms will be conducted sequentially to evaluate the combination of brentuximab vedotin and ipilimumab, brentuximab vedotin and nivolumab, and the triplet combination of brentuximab vedotin, ipilimumab and nivolumab, in patients with relapsed/refractory Hodgkin lymphoma.

For the combination of brentuximab vedotin and ipilimumab, a modified 3+3 dose escalation design will be used. Three to six patients will be tested at each dose level, and dose escalation will only occur after six patients are treated at the current dose level. For the combination of brentuximab vedotin and nivolumab, and the triplet combination of brentuximab vedotin, ipilimumab and nivolumab, a standard 3+3 dose escalation design will be used. The rule of dose escalation occurring only after six patients are treated is removed. All DLT are evaluated within the first cycle of treatment (1 cycle = 21 days). An expansion cohort (n=9) is planned for each arm once MTD is established.

9.1.2 Primary Endpoint

The primary endpoint is to determine the maximum tolerated dose (MTD) of each combination. One dose escalating level and one dose de-escalating level are planned for each combination. The dose levels being evaluated for each combination are given in the table below:

Dose level	Combination of brentuximab vedotin and ipilimumab		Combination of brentuximab vedotin and nivolumab		Triplet combination of brentuximab vedotin, ipilumumab, nivolumab **(Only if safety is confirmed in the other two combinations)**		
	Ipilimumab	Brentuximab vedotin	Nivolumab	Brentuximab vedotin	Nivolumab	Brentuximab vedotin	Ipilimumab
-1	0.3 mg/kg	1.8 mg/kg	1 mg/kg	1.2 mg/kg	1mg/kg	1.2mg/kg	1mg/kg
1	1 mg/kg	1.8 mg/kg	3 mg/kg	1.2 mg/kg	3mg/kg	1.2mg/kg	1mg/kg
2	3 mg/kg	1.8 mg/kg	3 mg/kg	1.8 mg/kg	3mg/kg	1.8mg/kg	1mg/kg
Expansion Cohort	MTD	MTD	MTD	MTD	MTD	MTD	MTD

9.1.3 Secondary Endpoints

Secondary endpoints include complete response (CR) rate, partial response (PR) rate, overall response (ORR) rate, duration of response (DOR), overall survival (OS) and progression-free survival (PFS). All these endpoints are defined in Section 6 and will be evaluated separately for each arm. Primary analysis of these endpoints will only include eligible patients who are treated at the MTD level and started protocol therapy. A secondary analysis including all treated patients is also planned. All response rates will be reported along with the 95% confidence intervals. DOR, PFS and

OS will be estimated using Kaplan-Meier methodology. Greenwood's formula will be used to calculate 95% confidence intervals for the Kaplan-Meier estimates.

DOR will also be estimated using Kaplan-Meier methodology. The DOR achieved with the most recent prior systemic therapy will be collected on the case report forms (CRFs), and descriptive statistics will be used to evaluate the DOR achieved with the protocol therapy and with the most recent prior systemic therapy.

9.1.4 Statistical Analysis Plan

MTD will be determined according to the rules outlined in protocol Section 5.1.

Dose limiting toxicities (DLT) are defined in Section 5. The table below summarizes the probabilities of dose escalation and de-escalation for a range of true DLT rates for the combination of brentuximab vedotin and ipilimumab, with a modified 3+3 design:

True DLT rate	10%	20%	30%	40%	50%
Probability of dose escalation	0.89	0.66	0.42	0.23	0.11
Probability of dose de-escalation	0.11	0.34	0.58	0.77	0.89

Because the dose escalation rule is slightly different for the combination of brentuximab vedotin, nivolumab and the triplet combination of brentuximab vedotin, ipilumumab, nivolumab, the probabilities of dose escalation and de-escalation, with a standard 3+3 design, for a range of true DLT rates for these combinations are:

True DLT rate	10%	20%	30%	40%	50%
Probability of dose escalation	0.91	0.71	0.49	0.31	0.17
Probability of dose de-escalation	0.09	0.29	0.51	0.69	0.83

Upon completion of the trial, frequency of subjects experiencing toxicities will be tabulated. Toxicities will be assessed and graded according to CTCAE v4.0 terminology for the phase I portion of this study. Exact 95% confidence intervals around the toxicity proportions will be calculated.

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A minimal of 18 patients and a maximum of 36 patients will be treated in the escalation portion of the study.

9.1.5 The expansion cohort and total sample size

Once the MTD has been reached, 9 additional patients will be treated in an expansion cohort (for a total of 15 patients on the MTD level) to better characterize the safety of this treatment combination. The following table lists the probability of detecting at least 1 DLT out of a total of 15 patients on the MTD level, under various true toxicity rates.

True DLT rate	1%	3%	5%	8%	10%
Probability of detecting >=1 DLT	0.14	0.37	0.54	0.71	0.79

Therefore, a minimum of 18 and a maximum of 63 patients are planned for the study. Allowing for 10% ineligibility and path exclusion rate, total accrual goal is 70 patients. Assuming an accrual rate of 1 patient per month, maximum accrual time is approximately 70 months.

9.1.6 Original statistical design

In the original design, only the combination of brentuximab vedotin and ipilimumab was included, and three dose levels of ipilimumab were planned to be evaluated: 1 mg/kg (level 1), and 3mg/kg (level 2) and 10mg/kg (level 3). During the course of the study, the study team was aware of an increase in reported adverse events associated with ipilimumab dose level of 10mg/kg from other studies. After discussion with NCI, the study team decided not to open dose level 3 (Addendum 6). Dose level 2 (3mg/kg) is the highest dose level.

9.1.7 Monitoring Plan

The study is ongoing, the study team will meet weekly via teleconference to review and discuss DLTs and the overall trial conduct.

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9.2 Phase II

9.2.1 Study Design and Objectives

The phase II component is a randomized Phase II study between Brentuximab-Nivo and Brentuximab-Ipi-Nivo. Patients will be randomized at 1:1 ratio to Brentuximab-Nivo or Brentuximab-Ipi-Nivo arms, stratifying on prior BV vs. no prior BV. We will accrue 120 eligible patients to the phase II part. Considering a 5% ineligible rate, the total accrual will be approximately 126 patients. This phase II component will commence once the Brentuximab-Ipi-Nivo expansion cohort has completed (Arms G-I), and has met the pre-specified efficacy and toxicity criteria listed below.

- To meet pre-specified toxicity, the dose expansion cohort (Arm I) must be completed with no more than 33% (2 out of 9) patients demonstrating a DLT.
- To meet pre-specified efficacy criteria, Arms G-I must have a preliminary ORR of at least 60% and a CR rate of at least 40%.

9.2.2 Primary Endpoint and Sample Size Calculation

The primary endpoint will be complete response (CR) rate. Published phase II data suggest that the CR rate of BV is 34% and the CR rate of nivolumab is 8%. The CR rate of Brentuximab-Nivo is approximately 50% with investigator assessed response from the completed phase I part of this study. In the Phase II component, the study will be centrally reviewed so we are assigning a CR rate 10% lower for Brentuximab-Nivo of 40%. With n=120 (60 on each arm), the

study will have 85% power at one-sided 0.15 significance level (fisher's exact test) to detect a 20% improvement in CR rate from 40% with Brentuximab-Nivo to 60% with Brentuximab-Ipi-Nivo.

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9.2.3 Secondary Endpoints

ORR, PFS (or modified PFS) and OS will be used as secondary endpoints as well as the duration of response (DOR). All tumor assessments will be made using Revised Response (Cheson) and Deauville criteria. Immune response criteria are included for reference only in the Appendix. Progression-free survival (PFS) is defined as the time from randomization to documented lymphoma progression or death from any cause, whichever occurs first. Patients who have not experienced an event of interest by the time of analysis will be censored at the date they are last known to be alive and progression-free. During therapy, progression free survival will be documented with appropriate scan (e.g., PET/CT scan). In follow-up after treatment scans are very infrequent; twice annually in year 1 of follow-up and once annually in year 2. There are no further scans beyond year 2. In follow-up when a scan is not available progression-free survival status will be updated based on physician exam documenting that the patient is free of any signs/symptoms of recurrence. Overall survival (OS) is defined as the time from randomization to death from any cause, and patients who are thought to be alive at the time of final analysis will be censored at the last date of contact. DOR is measured from the documented beginning of response (CR or PR) to the time of relapse. This is measured in responders.

We will further evaluate the safety and characterize the toxicity for the combinations of brentuximab vedotin and nivolumab, and brentuximab vedotin, ipilimumab, and nivolumab.

9.2.4 Statistical Analysis Plan

All primary and secondary endpoints will be evaluated and compared between two arms including eligible and treated (evaluable) patients. The exception to this includes the analysis of toxicity data, which include all patients who received any study treatment regardless of eligibility.

The analysis of CR and ORR between two arms will be performed using Cochran-Mantel-Haenszel (CMH) test stratifying on prior BV (Yes Vs. No). Multivariable logistic regression modeling will be used to adjust for the effect of any covariates that are associated with these categorical outcomes. DOR, PFS and OS will be estimated using Kaplan-Meier methodology and compared between arms usng stratified log-rank test. Greenwood's formula will be used to calculate 95% confidence intervals for the Kaplan-Meier estimates. Cox proportional regression model will be used to estimate hazard ratios (95% CI) and assess the relationship between other prognostic factors with time-to-event outcome. Point estimates of all endpoints will be accompanied by the corresponding 90% confidence intervals.

DOR will also be estimated using Kaplan-Meier methodology. The DOR achieved with the most recent prior systemic therapy will be collected on the case report forms (CRFs), and descriptive statistics will be used to evaluate the DOR achieved with the protocol therapy and with the most recent prior systemic therapy.

In the event that there are missing data, no imputation of the missing data will be conducted. We will assume that data are missing at random and will conduct all analyses as originally planned. We do not anticipate an excess of missing data.

Subset analyses are planned for the stratification factor and all known prognostic factors. Subset analyses of all variables, including correlatives, are considered to be exploratory in nature.

9.2.5 Projected accrual and follow-up

The study will accrue 126 patients which will lead to about 120 eligible patients for the analysis. In phase I, we accrued 1-2 patients/month with the participation of limited institutions. With the study opening phase II throughout the NCTN network, we expect to accruel 3-4 patients/month. It is anticipated that the accrual period will be approximately 40 months. The study will be followed for an additional 5 years after last patient enrolled to the study. Therefore, the study duration is estimated to be 8-10 years, for reporting of secondary endpoints.

9.2.6 Randomization Scheme

Randomization to treatment will be determined using permuted blocks within strata (prior BV or not) with dynamic balancing on main ECOG-ACRIN institutions plus affiliates.

9.2.7 Monitoring Plan

Safety Monitoring

Toxicity will be assessed and reported on all patients who receive any protocol treatment regardless of eligibility status. Interim analyses of toxicity are performed twice yearly for all ECOG studies. Reports of these analyses are made available to the ECOG Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section **Error! Reference source not found.**. In addition, the ECOG-ACRIN AE monitoring system performs routine toxicity evaluation and a study will be flagged for toxicity review when any of the following occurs (i) a previously uncirculated Grade 5 AE, (ii) 2 reports in the past month, or (iii) 6 reports in the past 6 months of previously uncirculated Grade ≥ 3 AEs.

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Grade 3 and higher adverse events will be reviewed by the study team monthly. If there are >= 10% (2 or more) grade 5 events in the first 20 patients that are considered possibly, probably, or definitely related to therapy, the study will be suspended for a detailed review of all AEs. The probability of observing 2 or more Grade 5 treatment-related AEs among 20 patients given a true underlying Grade 5 AE

rate of 1%, 5%, 10%, 15%, and 20% is 1.7%, 26.4%, 60.8%, 82.4%, and 93.1% respectively.

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As per NCI CTCAE, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and classified as either "unrelated or unlikely to be related" to study treatment in the event of an actual relationship developing.

Futility Monitoring

This study will be monitored for both efficacy and futility. This will take place after 30 patients have been assessed for response on each arm, and without accrual suspension. Due to the delay in centrally reviewed response, the early look will use data based on investigator assessed response.

It is of interest to discontinue early an arm that does not have a signal of efficacy. An arm with ≤ 10 investigator-assessed CRs among 30 patients will be suspended. This translates to an observed CR rate of ≤ 33%. In the Phase I part of the study, we observed a CR rate of > 50% with BN based on investigator assessed response. If the true CR rate is 50% then there is only a 5% chance of suspending the treatment arm, whereas if the true CR rate is 25% then theprobability of suspending the arm is 89%.

For futility assessment, the CR rate will be compared between BNI and BN arms and the study will be suspended if the observed CR rate under BNI is not higher than that under BN.

9.3 Gender and Ethnicity

There has not been a previous study with relapsed/refractory Hodgkin lymphoma. The anticipated accrual in subgroups by gender and race given below is based on previous accrual data (within ECOG) from E2496 (previously untreated Hodgkin's disease).

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	9	9	18
Not Hispanic or Latino	81	90	171
Ethnic Category: Total of all subjects	90	99	189
Racial Category			
American Indian or Alaskan Native	0	1	1
Asian	1	1	2
Black or African American	9	9	18
Native Hawaiian or other Pacific Islander	0	1	0

White	80	87	168
Racial Category: Total of all subjects	90	99	189

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

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9.4 Correlative Endpoints in Phase I and Phase II

Analyses of the correlative endpoints will combine patients from both phase I and phase II and will be done for the eligible patients who are treated at the phase I MTD level or phase II (primary analysis) as well as for all treated eligible patients (secondary analysis). Given that the expected sample size is small, these analyses will be mainly exploratory and are not adjusted for multiple comparisons. Each combination will be evaluated separately. Assuming 70-80% patients have biomarker measurement available, the sample size is roughly 11-12 for brentuximab-ipi, and 53-60 for brentuximab-nivo and brentuximab-ipi-nivo combinations. The following power calculations are provided for brentuximab-nivo and brentuximab-ipi-nivo combinations.

9.4.1 Peripheral Blood Biomarkers

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In phase I, peripheral blood samples are collected at the following 4 time points: baseline (Time 1), day 1 of cycle 2 (Time 2), restaging of first PET/CT (Time 3), completion of study (Time 4).

In phase II, peripheral blood samples are collected at the following timepoints: Pre-cycle 1, pre-cycle 2, at first staging and then every 3 months including off study.

In evaluating the effect of the treatment combination on altering immunity, quantity of main interest is the change in the percentage of activated T cells and Natural Killer cells from Time 1 to Time 3, and from Time 2 or Time 3 to Time 4. These quantities of interest will be calculated for each patient and the Wilcoxon signed-rank test will be used to test for significant difference between the time points. Assuming two-sided Type I error of 0.1, the study will have 83% power to detect an effect size of 0.37 (difference as fraction of the standard deviation) with sample size of 53, and an effect size of 0.35 with sample size of 60. Based on Ansell et al, the estimated standard deviation of the percentage change from pre- to post-treatment (SDdiff) ranges from 3.4 to 7.5 across specific T cell phenotypes, the effect sizes of 0.37 and 0.35 are then translated to absolute differences of 1.2 to 2.8. Using Wilcoxon rank sum test (two-sided Type I error of 0.1), we will also evaluate between those who progress or die within one year vs. those who are event-free at one year. Assuming a 50% PFS rate at 1-year the 56 patients yield approximately 28 patients who fail at 1-year and 28 patients will be event-free at 1 year. The study will have 85% power to detect an effect size of 0.77 at two-sided 0.1 significance level. From Ansell et al, the estimated standard deviations (SD) of the activated T-cell percentages across reported time points range from 7.6 - 24.9 so an effect size of 0.77 correspond to absolute difference of 5.9 - 19.2. The

standard deviations and absolute differences are on the % scale (percentage of activated immune cells). In the case of smaller effect size and/or unbalanced group sample size the study will be under-powered and analyses will be mainly descriptive and exploratory.

It is also of interest to examine the treatment effect on the systemic immune phenotype by investigating a panel of cytokine and T cell specific biomarkers including: PD-1, Tim-3, ICOS, IL-10, IL-6, TARC, sCD30, galectin-1 and the peripheral blood absolute lymphocyte to monocyte ratio. Again, pre- and post-treatment levels of these markers will be compared using the Wilcoxon signed-rank test with two-sided Type I error of 0.1. Based on data available from Gaiolla et. al. and Weihrauch et. al. the standard deviations (SD) of the marker levels (on the log2 transformed scale) for IL-6, IL-10, and TARC range from 0.38 to 1.2. We estimate the standard deviations of the differences (SDdiff) of the log2 transformed marker levels between pre- and post-treatment to range from 0.087 to 0.86 assuming a correlation of 0.7 between the pre- and post-treatment measurements, therefore an effect size of 0.37 (83% power with 53 patients) is translated to a 1.0 fold change (SDdiff=0.087) to 1.24 fold change (SDdiff=0.86). In evaluating the marker levels between patients who fail at 1-year vs. patients who are event-free at 1-year, an effect size of 0.77 (85% power with 56 patients) is translated to 1.2 fold-change (SD=0.38) to 1.9 fold-change (SD=1.2). The analyses of PD-1, co-expression of Tim-3 with PD-1, ICOS, sCD30, galectin-1 and the peripheral blood absolute lymphocyte to monocyte ratio will be mainly exploratory and will be summarized descriptively at the time-points described above. The association with PFS will be explored.

9.4.2 Gene Expression Profiling (GEP)

We will identify differentially expressed genes between two groups (for example, patients who fail at 1-year vs. patients who are event-free at 1-year or responders vs. non-responders) using a rank-based method developed by Dr. Hong (RankProd, R package, Bioconductor Project) with multiple comparison adjustment using a false discovery rate (FDR) approach. A two-way unsupervised hierarchical clustering analysis will be applied to both the genes and the samples to illustrate whether GEP can separate two groups or is associated with other clinical factors. The genes ranked as most significant will be assessed by gene ontology and pathway analysis for their potential functions in lymphoma biology and treatment failure. Testing the association of gene sets with treatment outcome will be performed using Globaltest and Gene Set Enrichment Analysis (GSEA).

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9.4.3 Microbiome Analysis

Phenotype comparison. We will compare the gut microbiome between HL patients (n=120) and healthy controls (n=60) with respect to global diversity, taxonomic abundance, and bacterial functional pathways. Additionally, the clinical response for all HL patients will be examined by comparing the gut microbiome at different time points (baseline, mid-treatment, and completion) for responders and non-responders.

We will assess α-diversity using numbers of observed species (richness) and Shannon index in linear regression. β-diversity will be assessed using weighted and unweighted UniFrac distances matrices (Lozupone, Hamady et al. 2007). We will perform Permutational Multivariate Analysis of Variance (PERMANOVA) (McArdle and Anderson 2001) of the UniFrac distance to test differences in overall oral microbiome composition among different groups. The relative abundance of each taxon (phyla to genera) and functional pathways among different groups will be statistically compared in univariate analysis using t-test (or Wilcoxon test) and in multivariate analysis using logistic regression. Global diversity tests and multivariate analysis for taxonomic abundance and functional pathways will be adjusted for potential confounders (age, gender, race, and BMI) in the comparisons of HL patients and controls, and further adjusted for stage and grade when examining the clinical response among HL patients. To consider multiple testing, we will use the false discovery rate (FDR) based on the Benjamini and Hochberg method (Benjamini and Hochberg 1995). We will consider an FDR-adjusted p-value (q value) less than 0.10 as significant.

9.4.4 Imaging Correlative Study

For the phase II study, PET4 (PET after 4 cycles of therapy) and late time period at PET10 (PET after 10 cycles of therapy) image data will be evaluated using Lugano response criteria with various D 5PS cut-offs in the entire cohort and in different therapy cohorts to determine if the existing set of criteria is sufficient to segregate the group into various response categories.

At PET4 and PET10 time points, we will correlate PFS, EFS, OS with - Lugano-based response using D 5PS in two reading settings [1-3 (negative) vs 4-5 (positive) and D 5PS 1-4 (negative) vs. 5 (positive)] (KM curve and log-rank testing)

- Absolute SUVmax
- Metabolic whole body tumor volume (MTV) and tumor lesion glycolysis (TLG)
- % change in SUVmax, MTV and TLG between baseline and during therapy (PET4 and PET10)
- %change in size (SPD*) on CT
- Absolute CT tumor volumes
- %change in CT size (SPD) and in CT tumor volume between baseline and during therapy (PET4 and PET10)

  *SPD: sum of perpendicular diameters

9.4.4.1 Sample size consideration and power analysis

The sample size of the phase II study is 120 and the baseline FDG PET/CT scans will be available from 80% - 90% of the patients. Lugano-based response using D 5PS will be categorized into two groups, i.e., 1-3 (negative) vs 4-5 (positive) or 1-4 (negative) vs. 5 (positive). In this

imaging correlative study, we assume the association between imaging and patient's outcome will not depend on the treatment assignment. Patients treated under different treatments will be combined for the proposed analysis. Thus, the sample size is estimated to be between 96 and 108. As the current observed event rate is about 30% for progression-free survival, we assumed a 20% and 40% event rate for the negative and positive groups, respectively. The power analysis is based on the tests for survival outcome (PFS) between the dichotomized response groups (i.e., negative vs. positive). Table 1 shows the results of power analysis under various ratios of positives versus negatives after response dichotomization. The hazard ratio was assumed to be 2.5 between positives and negatives. The tests for two survival curves using Cox' proportional hazards model in PASS 14 was used for these computations.

Table 1: Power Analysis from testing two survival curves using Cox's proportional hazards model. Assumptions: one-sided test with 0.05 significance level, proportions of subjects having event during the study is assumed 0.20 for the negative group and 0.40 for the positive group.

Power	%Positive	%Negative	Hazard Ratio (+/-)
N = 96			
0.71	1/3	2/3	2.5
0.79	1/2	1/2	2.5
0.78	2/3	1/3	2.5
N = 108			
0.75	1/3	2/3	2.5
0.83	1/2	1/2	2.5
0.83	2/3	1/3	2.5

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10. Imaging Studies

ECOG-ACRIN plans to archive PET/CT image data obtained at study registry (relapse PET) and those collected during the course of the study at the central ACR Imaging Core Laboratory. In the future, the de-identified image archive may be used for additional research, such as retrospective reviews of disease or software validation. Patient identifiers will never be included in future research and no patients will be named in publications related to future research.

10.1 Standard-of-Care Imaging Time Points and Minimum Preferred Phases

10.1.1 All standard-of-care imaging studies (including CT, MRI, PET, or any combination), including all phases completed, will be submitted to ACRIN per Section 10.3 instructions.

10.1.2 Standard practice imaging studies for the trial per E4412 procedures include:

- Pre-treatment baseline scan ^{18}F-FDG Whole Body PET0;
- Interim ^{18}F-FDG Whole Body PET4 after cycle 4/before cycle 5 of treatment.
- ^{18}F-FDG Whole Body PET12 before cycle 13 of treatment.

10.1.3 Preferably, a minimum of three (3) image phases will be submitted (see below), as well as any dedicated contrast enhanced CT studies that may be performed as standard institutional practice.

10.2 Central Reader Study

Three standard practice ^{18}F-FDG Whole Body PET/CT imaging studies (pre-therapeutic baseline [PET0], interim PET after 4 cycles of therapy [PET4], and PET after 12 cycles of therapy [PET12]) scans will be archived and centrally reviewed at the American College of Radiology (ACR) Imaging Core Laboratory by ACRIN. Our primary imaging aims are as follows:

10.2.1 **Imaging Aim 1:** To evaluate atypical response patterns with currently available response evaluation criteria

10.2.2 **Imaging Aim 2:** To correlate response evaluated using currently available response evaluation criteria with duration of response (PFS, EFS, FFS)

10.2.3 **Imaging Aim 3:** To evaluate response patterns in different immunotherapy treatment schemes and correlate with historical data using chemotherapy

10.2.4 **Imaging Aim 3:** To correlate imaging changes in all treatment schemes quantitatively with PFS

Exploratory analyses are planned to evaluate correlation of imaging findings with therapeutic response and survivorship:

Measurements and Statistical Evaluations: Refer to Section 9.4.3

10.3 Images Submission

TRIAD 4.0 Submission: The method of image transfer employed by the E4412 trial is TRIAD v4.0, a software application that ACRIN provides for installation on a site's PC. One or several computers of choice within the institutional "firewall" and on the institutional network may be equipped with TRIAD 4.0 software; Internet access is also required. The TRIAD application can then be configured as a DICOM destination on either scanner(s) and/or PACS system for direct network transfer of study related images into the TRIAD directory. When properly configured, the TRIAD software anonymizes, encrypts, and performs a lossless compression of the images before they are transferred to the ACRIN image archive in Philadelphia. Once equipment-readiness has been determined, imaging personnel from ACRIN will coordinate installation and training for the software. At study start-up sites will receive TRIAD 4.0 software registration and installation information.

TRIAD 4.0 Installation Information and User Guide are available at: https://triadinstall.acr.org/triadclient/

Questions and general inquiries regarding TRIAD 4.0 can be sent to: triad-support@acr.org. Please include "E4412 Trial" in the subject line of all inquiries.

The submission of image data on media will not be accepted for the E4412 trial.

All image-related forms are found in the iMedidata Rave database used for the trial.

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11. Research Sample Submissions

Initial diagnostic and relapse tumor samples will be obtained and sent for central review. The optional research biopsies are to be submitted from consenting patients for laboratory research studies. These studies are defined in Sections 12.3 and 12.5. Peripheral blood is to be submitted from consenting patients for laboratory research studies. These studies are defined in Sections 12.1 and 12.2. Stool specimens are to be submitted from consenting patients for laboratory research studies. These studies are defined in Section 12.6.

The IRB approved consent must allow patients the option to provide samples for use in the optional laboratory research studies and for undefined future research studies. Failure to allow this option will result in a major violation at the time of an audit.

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (see Section 11.5). An STS shipping manifest form is to be included with every submission.

All samples must be labeled clearly with the ECOG-ACRIN protocol number (E4412), ECOG-ACRIN patient sequence number, patient's initials, date of collection and sample type.

11.1 Sample Collection and Submission Schedule

Samples are to be submitted as follows:

- Pathology samples from the initial diagnostic and confirmatory relapse biopsies are to be submitted within one (1) month following registration/randomization. Research biopsies are to be submitted within one (1) month of collection. See Section 11.2.

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- Peripheral blood samples are to be submitted as outlined in Section 11.3 on the day of collection. Samples are to be collected at the following time points:

  Phase I

  - Prior to the Start of Treatment
  - Day One (1) of Cycle Two (2) [prior to treatment]
  - Time of First Restaging PET/CT [+/- 5 days]
  - After Completion of Therapy or Off Treatment

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  Phase II

  - Prior to the Start of Treatment
  - Day One (1) of Cycle Two (2) [prior to treatment]
  - Time of First Restaging PET/CT [+/- 5 days]
  - Every Three (3) Months During Treatment [up to two years]
  - Grade Three (3) or Greater Toxicity
  - After Completion of Therapy or Off Treatment

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- Stool samples are to be submitted as outlined in Section 11.4 on the day of collection. Samples are to be collected at the following time points:
  - Prior to the Start of Treatment
  - Time of First Restaging PET/CT [+/- 5 days]

- Month 9 During Treatment
- After Completion of Therapy or Off Treatment

11.2 Submissions to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF)

Submitting pathologist and clinical research associate may refer to Appendix I which outlines the Pathology Submission Guidelines.

Submission of pathology materials is mandatory for central diagnostic review, failure to submit the required materials may render the patient's data unevaluable.

The tissue samples are to be labeled with the institution's assigned pathology ID# as well as the information above.

11.2.1 Required Materials

Forms: Must be submitted with all tissue submissions.

- STS generated Shipping Manifest Form.
- Copy of the institutional pathology report.

Pathological Material Submissions:

11.2.1.1 Representative FFPE tumor tissue blocks from initial diagnosis and confirmatory relapse (MANDATORY)

NOTE: If a block is unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirements:

- One (1) H&E slide, and
- Twenty (20) 4 µm unstained air-dried plus slides, and
- One (1) or more core punches (minimum of 4mm diameter). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF (844-744-2420). Adequately label every slide and core submitted.

If these criteria cannot be met, please contact the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) (eacbpf@mdanderson.org) to obtain alternative submission requirements.

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NOTE: The tumor tissue biopsies will also be used for the optional laboratory research studies outlined in Section 12 for those patients who consent.

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11.2.1.2 From patients who consent at institutions that have met the guidelines outlined in Section 11.6. Biopsies which are not performed for clinical purposes, but only to collect research

specimens will be reimbursed as outlined in Section 11.6 AND are not to be billed to insurance.

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Representative FFPE tumor tissue block from:

- On treatment core needle biopsy
- Off treatment core needle biopsy if not considered clinically necessary
- At time of first restaging for patients in PR, SD, or PD **(Phase II only)**

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NOTE: **Only blocks will be accepted from research biopsies eligible for reimbursement,** though institutions are allowed to keep an H&E slide.

11.2.2 Shipping Procedures

Pathology materials from the initial and relapse biopsies are to be shipped at ambient temperature within one (1) month following patient registration/randomization.

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Pathology materials from the research biopsies are to be shipped at ambient temperature within one (1) month following collection.

Ship using the CBPF's FedEx account using the FedEx on-line ship manager

Ship to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1. G1.3598
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

Access to the shipping account for shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center can only be obtained by logging onto fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org

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An STS shipping manifest form must be generated and shipped with all specimen submissions.

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11.3 Submissions to Mayo Clinic Lymphoma Laboratory

Blood samples should be shipped the day they are drawn. If you have any questions concerning sample collection and shipment, please contact Kim

Henderson at (507) 284-3805 or Henderson.Kimberly@mayo.edu at the Mayo Clinic Lymphoma Laboratory.

11.3.1 Sample Preparation Guidelines

Kits are available to order for collection of the samples, and will contain the supplies and instructions for collecting, processing, and shipping the samples. To order kits contact Kim Henderson at (507) 284-3805 or Henderson.Kimberly@mayo.edu Include the name of the contact person, phone number, address where the kits should be shipped, ECOG-ACRIN protocol number, the number of kits needed, and if the kits need to be shipped priority overnight, otherwise kitswill arrive in three to four working days.

The following CBC information must be entered into STS with each time point: WBC and lymphocyte count.

Blood samples should be shipped the day they are drawn at room temperature (do not freeze). Samples from multiple patients can be shipped together, but must be placed in separately labeled tubes and bags.

All samples must be clearly labeled with the ECOG-ACRIN protocol number E4412, the patient's initials (last name, first name), the patient's ECOG-ACRIN sequence number (If available), date of collection, and type of sample (PB).

- Peripheral blood: Draw 10mL of whole blood into each of six (6) green top tubes (provided in the kit) at each time point. Ship day of collection.

NOTE: Please completely fill all blood tubes as full as possible.

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NOTE: Collect 30 mL of whole blood into three (3) green top tubes any time patient has grade 3 or greater toxicity [Phase II only].

11.3.2 Shipping Procedures

Blood samples should be mailed the day they are obtained and shipped overnight to arrive during normal working hours. The laboratory is open to receive shipments Monday through Friday. Follow packing guidelines listed in the kit. If samples are sent late in the week and will arrive on the weekend, please note "Saturday Delivery" on the Federal Express form.

FRIDAY AND PRE-HOLIDAY SHIPMENTS SHOULD BE AVOIDED.

- Place the tubes in the absorbent holder and seal in the zip lock specimen bag.
- Place the filled specimen bag in the Styrofoam container.
- Loosely pack with paper toweling.
- Place the Styrofoam container and the Sample Tracking System Shipping Manifest Form within the cardboard mailing sleeve.

- Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx Air Bill and adhere to the exterior lid of the box. Ship specimens' priority overnight delivery the same day collected.
- Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

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If your shipment was not logged into the ECOG-ACRIN STS, please call Kim Henderson at (507) 284-3805 or e-mail Henderson.Kimberly@mayo.edu to notify the Mayo Clinic Lymphoma Laboratory when samples are being shipped. Indicate the ECOG-ACRIN protocol number, the FedEx tracking number, and the name and phone number of the contact person. The blood samples in prepared kits should be shipped to the following:

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Kim Henderson
Mayo Foundation
221 4th Avenue SW
613 Stabile
Rochester, MN 55905

An STS Shipping Manifest Form must be generated and shipped with all sample submissions.

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11.4 Submissions to New York University

Submit from patients who answer "*Yes*" to "*I agree to provide additional samples for research."*

Kits for the collection and shipment of the stool specimens are ordered online from Cenetron Central Laboratories. Instructions are provided in Appendix XX. Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000. Kits must be ordered after the patient has been randomized to the trial and will generally arrive within three (3) business days from when the order was placed.

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Patient should receive stool collection kit from institution prior to each time point and collect stool specimen 24-48 hours prior to each time point, refridgerate, and bring tube containing stool to institution.

11.4.1 Specimen Preparation Guidelines.

- Empty your bladder before beginning the collection. Collect fecal specimens free of urine and toilet paper.
- While holding the yellow tube top, unscrew ONLY the purple cap from the kit and set aside for later use.

Important:

Do NOT remove the yellow tube top.

Do NOT spill the stabilizing liquid in the tube.

- Use the spatula to collect a small amount of fecal specimen.
- Tranfer the fecal specimen into the yellow top tube. Repeat until the specimen fills the yellow top tube.

Important:

Do NOT push specimen into the tube.

- Scrape horizonatally across the tube top to level the specimen and remove any excess. Wipe exterior of tube and top with toilet paper or tissue as needed.
- Pick up the purple cap with the solid end facing down and screw onto the yellow top tube until tightly closed.
- Shake the sealed tube as hard and fast as possible in a back and forth motion for a minimum of 30 seconds.
- The fecal specimen will be mixed with the stabilizing liquid in the tube, not all particles will dissolve.

Important: Continue shaking if large particles remain.

- Place spatula in orginal packaging or wrap in toilet paper and discard in garbage.
- Refridgerate stool specimens until shipment in kit.

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11.4.2 Shipping Procedures

Stool specimens are to be shipped at ambient temperature Monday-Thursday via overnight courier within one (1) week of collection.

Please contact the laboratory to notify them of the shipment.

Ship using NYU's FedEx account number (8541-2318-1) to:

Emilia Cobbs
Department of Population Health
Division of Epidemiology
NYU Langone Health
522 First Avenue
Smilow Research Building, 12th Floor, Room 1206E
New York, NY 10016
Lab Phone: (212) 263-9226
Emilia.Cobbs@nyulangone.org

An STS shipping manifest form must be generated and shipped with all specimen submissions.

11.5 ECOG-ACRIN Sample Tracking System

It is **required** that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the specimens required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are

available by clicking this link:
http://www.ecog.org/general/stsinfo.html

Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated Shipping Manifest Form should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu.

Study Specific Notes

Generic Specimen Submission Form (#2981), along with the Mayo Clinic Patient Information Form (
Appendix VI) will be required only if STS is unavailable at time of specimen submission. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory. Indicate the appropriate Lab on the submission form:

- ECOG-ACRIN CBPF
- Mayo Clinic Lymphoma Laboratory
- New York University

Retroactively enter all specimen collection and shipping information when STS is available.

11.6 Institutional Reimbursements

11.6.1 Biopsy Reimbursements

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On treatment research biopsies will be obtained prior to cycle two (2). Off treatment biopsies will qualify for reimbursement in cases where the biopsy is not considered clinically necessary. Research biopsies obtained at the time of the first restaging for patients with PR, SD, or PD for phase II patients only. The biopsies are reimbursable up to a maximum of $3,750 for CT guided core needle biopsies and $3,100 for US guided core needle biopsies.

All institutions are eligible for the reimbursement for the research biopsies. However, it is up to the institution to set up the mechanism for the 'billing' of these biopsies. ECOG-ACRIN recommends billing the Principal Investigator (PI) of the institution.

Please note that blocks **MUST** be submitted in order to receive the reimbursement. Since these biopsies are being performed strictly for the research for this trial, blocks are required to be submitted in order to receive the reimbursement.

Prior to recruiting patients to the research biopsy portion, the following conditions must be met:

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a. The research rate of $3,750 for CT guided core needle biopsies and $3,100 for US guided core needle biopsies are deemed acceptable by the IRB or central research office.

b. The research rate is reported to the institution's financial office and an account established in the institution's principal investigator's name.

c. The patient provides written consent to undergo the additional biopsy.

NOTE: If the above rates are not accepted by your central research office do not present this additional research biopsy option to your patients.

Receipt of the biopsies will be verified prior to the release of any funds. Expenses for biopsies will be paid only to participating institutions, not to any other persons or entities, at the stated research rates outlined above.

NOTE: Neither patients nor their insurance companies are to be billed for the collection or submission of these research biopsies.

Distribution of the reimbursements requires:

- Submission of the requested biopsy sample using the ECOG-ACRIN Sample Tracking System (STS)
- Receipt and verification of the requested biopsy sample by the ECOG-ACRIN Central Biorepository and Pathology Facility via the ECOG-ACRIN STS. (Refer to Section 11.5 for STS requirements)
- Receipt of E4412 Biopsy Reimbursement Form (Appendix XII) to the ECOG-ACRIN Operations Office - Boston.

Reimbursements will be paid from the ECOG-ACRIN Operations Office - Boston to the ECOG-ACRIN Principal Investigator (PI) of the submitting ECOG-ACRIN institution.

Payments are made annually.

11.7 Use of Specimens in Research

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Pathological materials and peripheral blood and stool specimens will be distributed to investigators for central diagnostic review and laboratory research studies defined in Section 12.

Specimens from patients who consented to allow their specimens to be used for future ECOG-ACRIN approved research studies will be retained in an ECOG-ACRIN designated central repository.

Specimens submitted will be processed to maximize their utility for current and future research projects. Tissue processing may include, but is not limited to, extraction of DNA and RNA and construction of tissue microarrays (TMAs). DNA and plasma (if appropriate) will be isolated from the submitted peripheral blood specimens.

Any residual blocks will be available for purposes of individual patient management on specific written request.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future research study. Pathology

materials may be retained for documentation purposes or returned to the site. All other specimens will be destroyed per guidelines of the respective repository.

11.8 Sample Inventory Submission Guidelines

Inventories of all samples submitted from institutions will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of samples forwarded and utilized for approved laboratory research studies will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

12. Correlative Studies

The results of these studies are for the purposes of the trial only and will not be returned to the site or reported to the patient.

Processing of blood samples will occur in the Mayo Clinic Lymphoma Laboratory. Peripheral blood samples will undergo processing within 24 hours of collection. Peripheral blood will undergo separation of plasma and serum from peripheral blood mononuclear cells (PMBC), FICOLL centrifugation, and cryopreservation via standard operating procedures.

12.1 Evaluate the Ability of the Combination of Brentuximab Vedotin, Nivolumab, and Ipilimumab to Alter Tumor Specific T-Cell Immunity (Phase I and II)

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This laboratory research study will utilize blood samples submitted from consenting patients.

This analysis will be performed at the New York University Immune Monitoring Core under the direction of Dr. Catherine Diefenbach.

Preclinical and clinical observations suggest that antigen-primed memory T cells may be activated following administration of blocking anti-CTLA-4 antibodies (50, 51). Ansell et al. have previously demonstrated that an increase in the percentage of CD4+ cells with an activated memory T cell phenotype (CD3+, HLA-DR+, CD45RO+, and CD62Llow) in the biopsies of patients with both indolent and aggressive B-cell lymphomas was significantly correlated with favorable patient outcome (58). In HL the contribution of regulatory T cell subsets to disease biology and clinical outcome is an area of active research.

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Dr. Diefenbach has previously demonstrated that HL patients demonstrate evidence of chronic activation/exhaustion in circulating T cell subsets, as well as systemic perturbation of the monocyte-dendritic cell axis (93, 94). For the phase II portion of the study, this will be the largest set of HL patients investigated prospectively for biomarkers of immune activation treated on immunotherapy and as such would be an extremely valuable data for elucidating the differences in degree of clinical response (complete versus partial response) and duration of response.

12.1.1 Hypothesis

We hypothesize that the combination of brentixumab vedotin and ipilimumab will activate anti-tumor immune effector cells, and that this activation may correlate with clinical response.

12.1.2 Methods

We will evaluate patient peripheral blood samples collected prior to, during and subsequent to treatment following the assays described previously by Ansell (57). Using flow cytometry, ELISA, and ELISPOT we will:

a) Quantify the immunophenotype and activation state of tumor-infiltrating and peripheral blood T cells,

b) Evaluate tumor-specific T cell activity in peripheral blood lymphocytes,

c) Evaluate whether therapy augments the activity of memory T cells to recall antigens or promotes anti-tumor antibody production.

T cell Subsets

Cells will be stained with antibodies to identify T cells (CD3, CD4, andCD8), HL cells (CD30), cytokines (IFNγ and IL-4), and T regs (CD25, and Foxp3). Cells will be acquired using the LSR II flow cytometer (BD). Compensation (parallel controls using cells singly stained for each color) and data analysis will be performed using FlowJo flow cytometry analysis software (TreeStar). The percentage and/or mean fluorescence intensity (MFI) of CD4+ and CD25+ or CD4+ FoxP3+ cells, as well as the percentage of IFNγ secreting T cells, will be compared to isotype controls to establish baseline values.

Influence of Tregs on CD8 Proliferation

Patient CD8+ T cells labeled with CFSE will be isolated and cultured either alone or with autologous anti-tumoral Treg cells with or without ipilimumab at ratios of 2:1 and 5:1. Cell proliferation will be evaluated by CFSE labeling and T cell proliferation assay (64).

Cytokine Release

Supernatants from both TH and THI co-cultures will be evaluated at several time points for cytokine release profiles using ELISA or multiplex kits (Invitrogen) on a Luminex 200 system. T cell activation as a function of IFNγ secretion will be simultaneously evaluated by flow cytometry.

Response to Recall Antigen

KLH-specific T cell proliferation will be measured as previously described(65).

Rev. Add16

12.2 Evaluate a panel of cytokine biomarkers from the peripheral blood as a potential immune signature of treatment response to therapy with brentuximab vedotin and ipilimumab and nivolumab for patients with relapsed / refractory HL (Phase I and II)

Rev. Add20

This laboratory research study will utilize blood samples submitted from consenting patients.

This analysis will be performed at the New York University Immune Monitoring Core under the direction of Dr. Catherine Diefenbach.

12.2.1 Background/Justification

As described in detail above many peripheral blood biomarkers associated with clinical outcome have recently been described. Most studies have evaluated these biomarkers retrospectively, or in small scale clinical trials, and to date most have been evaluated individually rather than in combination.

12.2.2 Hypothesis

Rev. Add16

We hypothesize that a constellation of cytokine biomarkers evaluated from the peripheral blood may constitute an immune signature for clinical response vs. refractory disease. The levels of these biomarkers will be elevated pre-treatment, will decline significantly during therapy in responders, and may become a predictor of treatment response that is more easily evaluable, less expensive, and more precise than PET/CT, the current standard biomarker of treatment response.

12.2.3 Methods

Using flow cytometry, Luminex, and ELISA technology we will investigate a) peripheral blood T cell expression of programmed death ligand-1 (PD-1), T cell immunoglobulin and mucin domain-containing protein 3 (Tim-3), and inducible T-cell costimulator (ICOS) , b) peripheral blood levels of the cytokines and proteins IL2R, IL-10 and IL-6, TARC, soluble CD30 (sCD30), and galectin-1,and c) the peripheral blood absolute lymphocyte/monocyte ratio from a standard laboratory differential panel.

Rev. Add16

During the phase II portion of the study, serum cytokines/chemokines will be measured in a multiplexed platform to identify pharmacodynamic immune profiles associated with clinical outcome (baseline and on-study collections). In addition, baseline serum cytokine/chemokine profiles will be evaluated to potentially inform about pre-treatment characteristics with predictive/prognostic value.

12.3 HAHA Antibodies (Phase I only)

Rev. 9/16, Add16

This laboratory research study is a component of the immune analysis described in Section 12.2.

Rev. Add20

This laboratory research study will utilize blood samples submitted from consenting patients and will not require additional blood samples beyond what is collected for the immune analysis described in Section 12.2.

This analysis will be performed by Covance.

At the onset of this trial an increased number of infusion reactions to brentuximab vedotin were seen compared to baseline. These reactions generally occurred in cycle 2 or 3, in some but not all patients. With premedication these infusion reactions are no longer an issue, and no patient was required to discontinue therapy. However, we would like to investigate whether the generation of HAHA antibodies is occurring in patients, and whether these HAHA antibodies, if they occurred, were associated with these reactions.

This analysis will be primarily descriptive where the presence or absence of HAHA antibodies will be compared between pre-treatment and on-treatment plasma samples in a binary (yes/no) fashion. This will be reported descriptively given the small sample size.

We hypothesize that the generation of HAHA antibodies is not a consequence of treatment with this combination, and is not the mechanism underlying infusion reactions in a small fraction of patients.

12.4 Pathology Review (MANDATORY)

The appropriate representative tumor tissue samples will be forwarded to Dr. Natkunam for central diagnostic review and classification to confirm the diagnosis. This is a retrospective review to determine the evaluability of the patient's data for analysis. The results of the review are for the purposes of the trial only and will not be returned to the site.

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12.5 To evaluate using gene expression profiling (GEP) a signature of response to the novel combination of an antibody drug conjugate with immunomodulatory therapy.

This laboratory research study will utilize tumor tissue biopsy samples submitted from patients who answer "Yes" to "*I agree to participate in the laboratory research studies that are being done as part of this clinical trial."*

This analysis will be performed at the British Columbia Cancer Agency under the direction of Dr. David Scott and Dr. Christian Steidl.

12.5.1 Background

The Gascoyne laboratory and Christian Steidl have published extensively on immunhistochemical and GEP biomarkers of clinical outcome for early and advanced stage HL patients being treated with standard therapies. Steidl et al. recently examined microdissected HRS cells from 29 HL patients. Using integrative analysis tools they identified target genes with expression levels that significantly correlated with genomic copy number changes in primary HRS cells, and found a macrophage signature CSF1R that was significantly correlated with treatment failure in an independent set of 132 patients assessed by mRNA in situ hybridization. In multivariate analysis a combined score of CSF1R and CD68 high was an independent predictor of poor PFS (53). Recently using NanoString technology a gene expression based predictor, applicable to routinely available FFPE biopsies has been described which identifies high risk patients from a cohort of advanced stage cHL patients (54). To date these strategies have not been applied to patients receiving non-conventional or immunomodulatory therapies. Additionally these studies have been retrospective, with no patients providing on- and off- treatment biopsies that allowed the assessment of real time changes in the tumor microenvironment in response to therapy.

12.5.2 Hypothesis

In this proof of concept study we hypothesize that immunhistochemical and GEP biomarkers will suggest a signal for response to this immune-chemotherapy platform. The primary goal of this aim is feasibility, both with regard to biopsy collection and the assays that will justify this aim in larger randomized phase 2 clinical trials.

12.5.3 Methods

Patients will provide original tumor blocks from both their initial and relapse confirmatory biopsy. In consenting patients with easily

evaluable tumor a core needle biopsy will be performed immediately (+/- 7 days) prior to cycle 2, and if patients come off treatment. In collaboration with Christian Steidl and Randy Gascoyne we will evaluate by immunohistochemistry and gene expression profiling in tumor biopsies (initial, relapse confirmatory), prior to cycle 2, and off treatment (optional), changes in the tumor microenvironment including but not limited to T cell subsets, macrophages, and expression of cell surface markers such as PD-1/PDL-1. We will build a tissue microarray containing the initial biopsy specimens of patients, their biopsy obtained to confirm relapse, their intra-treatment biopsies, and off treatment biopises. We will perform immunohistochemistry (IHC), fluorescence-*in situ* hybridization (FISH), and RNA-*in situ* hybridization (RNA ISH) for markers known to be prognostic at diagnosis including but not limited to CD68+ macrophages, Th2 and Treg cells, and expression of PD-1/PDL-1. We hypothesize that the original biopsy specimens of these relapsed patients may be enriched for dysfunctional T cell subsets, and cellular components expressing prognostic markers. Moreover we hypothesize that the expression of these markers may be higher at the time of relapse than at initial diagnosis, and that the responders will demonstrate an alteration in these parameters in contrast to the non-responders, which may allow us to determine an immune signature of the tumor microenvironment that is predictive of clinical outcome. If confirmed, these exploratory analyses can be validated in larger patient samples or larger scale clinical trials.

We will perform medium-density, gene-expression profiling of formalin fixed paraffin embedded tissue (FFPE) samples obtained from initial diagnosis, relapse, and in consenting patients on- and off- treatment biopsies, using the NanoString technology which has been validated in the Steidl laboratory (54-56) to investigate the composition of the tumor microenvironment including but not limited to T cell subsets and macrophages. This technology allows the quantification of up to 800 mRNA species, simultaneously, with a no-enzyme, no-amplification technique. The hybridization target size of 100 nucleotides makes NanoString an ideal technology for FFPE-derived RNA that typically is fragmented. This exploratory aim may produce a multigene expression-based microenvironment immune signature which is a predictor of outcomes to treatment at relapse in relapsed/refractory HL. This finding may then be validated in larger patient samples or larger scale clinical trials. If additional fresh frozen material is available we will obtain this as well for microdissection analysis, however this not a study requirement.

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We will also examine a biopsy taken at the time of restaging for patients who have a PR who have accessible lesions to investigate differences between CR and PR patients in the tumor microenvirionment on treatment.

Rev. Add16

12.6 Lymphoma Microbiome (Phase II only)

12.6.1 Background

Rev. Add20

This laboratory research study will utilize stool samples submitted from consenting patients.

This analysis will be performed at the Ahn Laboratory at NYU Langone Health under the direction of Dr. Catherine Diefenbach and Dr Jiyoung Ahn.

We hypothesize that human gut microbiome dysbiosis influences HL lymphomagensis through the host immune responses. Commensal and pathogenic microbes are critical regulators of host inflammation and immunity. We showed that in Hodgkin lymphoma (HL), crosstalk between the tumor and its microenvironment alters systemic T cell phenotypes (Diefenbach, Sabado et al. 2011), and HL patients have evidence of chronic activation/exhaustion in their central memory and effector T cells (Diefenbach, Raphael et al. 2014). Animal studies suggest that intestinal microbiota can affect lymphomagenesis via direct effects on signaling, by mutagenesis secondary to increased production of reactive oxygen species, or by differentially altering circulating immune cells, resulting in modulation of the tumor microenvironment (Iida, Dzutsev et al. 2013, Viaud, Saccheri et al. 2013, Yamamoto and Schiestl 2014). In humans, the specific microbes *H. pylori and hepatitis C virus (HCV)* have been implicated in lymphoma pathogenesis[5]. Other examples of microbe induced lymphoid malignancies include: low-grade lymphomas associated with bacteria such as *C. jejuni, B. burgdorferi* and hepatitis C and HIV induced B cell lymphomas. In low-grade lymphomas associated with active hepatitis C, effective treatment of hepatitis C may result in spontaneous remissions, without further chemotherapy (Arcaini, Merli et al. 2012). However, there is a current research gap; data is lacking to connect the human gut microbiome (including bacteria, DNA virus, and fungus), B cell HL behavior, and T-cell exhaustion.

We propose an innovative study of gut microbiome, human immunity, and HL. From this unique resource, we will test the following hypothesis

12.6.2 Hypothesis

In this exploratory pilot study, we hypothesize 1) The gut microbiome in HL patients is less diverse with different flora composition than the gut microbiome of healthy controls, and that 2) gut microbiota profiles may correlate with clinical responses related to HL immunotherapy.

12.6.3 Methods

Stool collection and demographic/clinical data. Demographic information is obtained in screening. Participants collect stool at home, and may bring to their scheduled appointment or mail the stool kit to the Ahn research laboratory at NYU. Fecal samples will be collected from HL patients at different time points during the treatment. Healthy controls will be selected from the stored samples

using the same collection method in the database in the Ahn lab at NYU.

Full metagenome shotgun sequencing. We will extract genomic DNA from fecal samples using the PowerLyzer PowerSoil Kit (MO Bio Laboratory INC., Ca). DNA will be sheared using Covaris Adaptive Focused Acoustics, and fragments for amplification (200–300 bp) selected. We will use the ThruPLEX DNA-seq kit (Rubicon Genomics, MI) to prepare indexed shotgun libraries, following manufacturer's protocol. Libraries will be purified, quantified, pooled in equal molarity, and sequenced with 300-cycles (2 × 151 bp) on the Illumina HiSeq 4000.

Sequence reads pre-processing. Reads will be demultiplexed, and Trimmomatic (Bolger, Lohse et al. 2014) will then be used for read length filtering and trimming of Illumina adapter sequences and low-quality read ends. Reads mapping to the human genome will be identified using Bowtie 2 (Langmead and Salzberg 2012) and informatically removed. Forward and reverse paired reads are then concatenated for input into taxonomic and functional profilers MetaPhlAn2 (Segata, Waldron et al. 2012) and HUMAnN2 (Abubucker, Segata et al. 2012), designed for inputs of quality-filtered short sequence reads (i.e. from Illumina platforms), without requiring metagenome assembly. HUMAnN2 maps metagenomic reads to functionally annotated bacterial species genomes, and uses a translated search to align unmapped reads to UniRef protein clusters (gene families)(Suzek, Huang et al. 2007). These gene families are then grouped into MetaCyc pathways (Caspi, Bilington et al, 2015) using MinPath (Ye and Doak, 2009). In this way, HUMAnN2 determines gene family and functional pathway relative abundance within a metagenomic community. Shotgun reads will also be assigned taxonomic identity with MetaPhlAn2 (Segata, Ballarini et al, 2012), a taxonomic profiler designed for inputs of quality-filtered short sequence reads (i.e. from Illumina technology), without requiring metagenome assembly. This tool uses a set of ~1 million clade-specific markers (average 184 marker genes for each species) from >7,500 species to unequivocally identify and quantify specific microbial clades at the species level or higher.

Phenotype comparison. We will compare the gut microbiome between HL patients (n=120) and healthy controls (n=60) with respect to global diversity, taxonomic abundance, and bacterial functional pathways. Additionally, the clinical response for all HL patients will be examined by comparing the gut microbiome at different time points (baseline, mid-treatment, and completion) for responders and non-responders. We will assess α-diversity using numbers of observed species (richness) and Shannon index in linear regression. β-diversity will be assessed using weighted and unweighted UniFrac distances matrices (Lozupone, Hamady et al. 2007). We will perform Permutational Multivariate Analysis of Variance (PERMANOVA) (McArdle and Anderson 2001) of the UniFrac distance to test differences in overall oral microbiome composition among different groups. The relative

abundance of each taxon (phyla to genera) and functional pathways among different groups will be statistically compared in univariate analysis using t-test (or Wilcoxon test) and in multivariate analysis using logistic regression. Global diversity tests and multivariate analysis for taxonomic abundance and functional pathways will be adjusted for potential confounders (age, gender, race, and BMI) in the comparisons of HL patients and controls, and further adjusted for stage and grade when examining the clinical response among HL patients. To consider multiple testing, we will use the false discovery rate (FDR) based on the Benjamini and Hochberg method (Benjamini and Hochberg 1995). We will consider an FDR-adjusted *p*-value (q value) less than 0.10 as significant.

12.7 Plasma Cytokines/Chemokines Profiling

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This laboratory research study will utilize blood samples submitted from consenting patients.

This analysis will be performed at Myriad Rules-Based Medicine.

A small amount [0.5-1mL] of plasma per each time point will additionally be profiled at Myriad Rules-Based Medicine (RBM). Plasma cytokines/chemokines will be measured in a multiplexed platform to identify pharmacodynamic immune profiles associated with clinical outcome (baseline and on study collections). In addition, baseline plasma cytokine/chemokine profiles will be evaluated to potentially inform about pretreatment characteristics with predictive/prognostic value.

12.8 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secure data transfer to the ECOG-ACRIN Operations Office - Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the investigator.

Rev. Add16 **13. Electronic Data Capture**

Please refer to the E4412 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office - Boston to CTEP by electronic means.

13.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG-ACRIN Operations Office - Boston prior to destroying any source documents.

14. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

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A Phase I Study with an Expansion Cohort/Randomized Phase II Study of the Combinations of Ipilimumab, Nivolumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma

Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. Instructional memo to submitting pathologists
2. List of Required Materials for E4412

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3. ECOG-ACRIN Generic Specimen Submission Form (#2981)

Rev. 1/15, Add16

List of Required Material

E4412	A Phase I Study with an Expansion Cohort of the Combination of Ipilimumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma

The following materials are to be submitted within one (1) month of registering/randomizing the patient to the trial:

1. Pathology materials (MANDATORY for central diagnostic review):

   Representative FFPE tumor tissue blocks from initial diagnosis and confirmatory relapse.

   NOTE: If a block is unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirements:

   - One (1) H&E slide, and
   - Twenty (20) 4 µm unstained air-dried plus slides, and
   - One (1) or more core punches (minimum of 4mm diameter). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF (844-744-2420). Adequately label every slide and core submitted.

   - If these criteria cannot be met, please contact the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) (eacbpf@mdanderson.org) to obtain alternative submission requirements.

The following materials are to be submitted within one (1) month of collection:

2. Pathology materials:

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   Representative FFPE tumor tissue block from on- and off- treatment biopsies and biopsy at the time of restaging from patients with PR, SD, or PD [Phase II only].

   NOTE: **Only blocks will be accepted for research biopsies,** though sites are allowed to keep an H&E slide.

   NOTE: Since blocks are being used for laboratory research studies, in some cases the material may be depleted and, therefore, the block may not be returned.

3. Forms and Reports:

   The following items are to be included with the pathology materials:

   - Institutional Pathology Report
   - ECOG-ACRIN Generic Specimen Submission Form (#2981) if STS is unavailable
   - ECOG-ACRIN Sample Tracking System (STS) Shipping Manifest Form

   NOTE: Adequate patient identifying information must be included with every submission. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials, and will help to expedite any required communications with the institution (including site pathologists).

4. Mail pathology materials to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1. 3598
1515 Holcombe Blvd
Houston, TX 77030

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility by telephone Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites) or email eacbpf@mdanderson.org.

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MEMORANDUM

TO: (Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE:

SUBJECT: Submission of Pathology Materials for E4412: A Phase I Study with an Expansion Cohort of the Combination of Ipilimumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by_____(ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for pathology review and laboratory research studies.

Return the surgical pathology report(s), the slides and/or blocks and any other required material (see List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG-ACRIN Central Biorepository and Pathology Facility.

Blocks and/or slides submitted for this study will be retained at the ECOG-ACRIN Central Repository for undefined future research studies. Paraffin blocks will be returned upon written request for purposes of patient management.

Please note: Since blocks are being used for laboratory research studies, in some cases the material may be depleted, and, therefore, the block may not be returned.

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility at 1-844-744-2420 or eacbpf@mdanderson.org.

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address:_____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time-point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last_____First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name)_____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name_____ **CRA Phone**_____ **CRA Email** _____

Comments

9/12/14

A Phase I Study with an Expansion Cohort/Randomized Phase II Study of the Combinations of Ipilimumab, Nivolumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma

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Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the help of people like you who participate in clinical trials, we will improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the Eastern Cooperative Oncology Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

A Phase I Study with an Expansion Cohort/Randomized Phase II Study of the Combinations of Ipilimumab, Nivolumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma

Appendix III

CRADA/CTA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator"
Rev. 8/14 (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

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6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

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Appendix IV

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

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Appendix V

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on ipilimumab, nivolumab and/or brentuximab vedotin , or within 28 days of the patient's last dose of ipilimumab, nivolumab and/or brentuximab vedotin must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP's Adverse Event Reporting System (CTEP-AERS) (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm)

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERS report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERS report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status via CTEP-AERS.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office - Boston. Please contact the ECOG-ACRIN Operations Office - Boston to ask for a conference call to be set up with the appropriate individuals.
- It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an amendment to the initial CTEP-AERS report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a new CTEP-AERS report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the CTEP-AEMD Help Desk at 301-897-7497 or aemd@tech-res.com, for it will need to be discussed on a case by case basis.

Rev. Add17 **Reporting a Pregnancy Loss**

A pregnancy loss is defined in CTCAE as "*Death in utero.*"

It must be reported via CTEP-AERS as Grade 4 "*Pregnancy Loss*" under the System Organ Class (SOC) "*Pregnancy, puerperium and perinatal conditions"*.

A pregnancy loss should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death

Reporting a Neonatal Death

A neonatal death is defined in CTCAE as "*A death occurring during the first 28 days after birth*" that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported via CTEP-AERS AND any infant death after 28 days that is suspected of being related to the *in utero* exposure to ipilimumab, nivolumab and/or brentuximab vedotin must also be reported via CTEP-AERS.

It must be reported via CTEP-AERS as Grade 4 "*Death neonatal*" under the System Organ Class (SOC) "General disorder and administration site conditions".

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

Additional Required Forms:

When submitting CTEP-AERS reports for pregnancy, pregnancy loss, or neonatal loss, the **CTEP *'Pregnancy Information Form'*** must be completed and faxed along with any additional medical information to CTEP (301-230-0159). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

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Appendix VI

Blood Collection Kit Mayo Clinic Lymphoma Laboratory

Specimen Checklist and Shipping Instructions

****PLEASE AVOID DRAWING OR SENDING SPECIMENS ON FRIDAYS AND HOLIDAYS****

Kit Contents:

- Small Styrofoam box and cardboard mailing sleeve
- Patient Information Form
- FedEx Air Bill with pre-printed return address
- 10mL Green Top collection tubes
- Absorbent tube holder
- Zip lock specimen bag

Packing and Shipping Instructions:

1. Collect the following specimens:
    1. Peripheral blood – Draw:
        - 60mL into six (6) Green Top tubes

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NOTE: *Collect 30mL of whole blood into three (3) Green Top tubes any time patient has a grade 3 or larger toxicity (Phase II oly)*

2. All specimens are to be clearly labeled with the ECOG-ACRIN protocol number E4412, the patient's initials (last, first, middle), ECOG-ACRIN sequence number (if available) and date of collection.
3. Place the tubes in the absorbent holder and seal in the zip lock specimen bag.
4. Place the filled specimen bag in the Styrofoam container.
5. Loosely pack with paper toweling.
6. Place the Styrofoam container and the Sample Tracking System Shipping Manifest Form within the cardboard mailing sleeve.
7. Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx Air Bill and adhere to the exterior lid of the box. Ship specimens via priority overnight delivery (next day delivery by 10am) the same day collected.
8. Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

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The ECOG-ACRIN Sample Tracking System will automatically contact the Lymphoma Laboratory. If your patient has not yet been registered and/or you did not use the ECOG-ACRIN Sample Tracking System, please call Kim Henderson at (507) 284-3805 or e-mail Henderson.Kimberly@mayo.edu to notify the laboratory when specimens are being shipped. Indicate the ECOG-ACRIN protocol number, the Fed Ex tracking number, name and phone

number of the contact person. The blood specimens in prepared kits should be shipped to the following:

Rev. Add16

Kim Henderson
Mayo Clinic Lymphoma Laboratory
221 4th Avenue SW
613 Stabile
Rochester, MN 55905

Patient Information Form

Specimen Date: / /

Patient Initials (last name, first name):

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ECOG-ACRIN Protocol #: E4412

ECOG-ACRIN Patient Sequence #:

Contact Person:

Institution:

Address:

City State Zip

Phone #:

FAX #:

Rev. Add16 Please indicate which specimens are being shipped at this time:

2. Prior to Start of Treatment
3. Day One of Cycle Two
4. Time of First Restaging PET/CT
5. During Treatment (Phase II only)
6. Grade Three or Greater Toxicity (Phase II only)
7. After Completion of Therapy
8. Off Treatment

Any questions concerning these specimens or to obtain blood collection kits for the E4412 study, please contact:

Kim Henderson
Mayo Clinic Lymphoma Laboratory
(507) 284-3805
Henderson.Kimberly@mayo.edu

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Appendix VII
E4412 Biopsy Reimbursement Form

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This form is to be used to request reimbursements for the performance and submission of the **non-SOC** biopsies as outlined in Section 11. Reimbursements are NOT applicable for biopsies performed as part of standard of care, and thus billed to patients or their insurance.

If you have questions about the reimbursement process, please contact the EA funding team at ea.fundingsheet@jimmy.harvard.edu.
Please fax the completed form to the ECOG-ACRIN Translational Science Team (TST), FAX: (617) 589-0914

Payee Address	
Payee/W-9 Name:	
Payee Tax ID #:	
Attention To:	
Street Address:	
City, State, Zip:	
Any Requested Reference on Payment (i.e. Invoice #):	

Institution CTEP ID:	
Name of Investigator:	
NCI Investigator ID #:	

	ECOG-ACRIN Case ID	**Time Point**	**Date of Service**	**Service Performed (CT or US Guided)**	**Amount Requested**
#1					$3,750.00 (CT guided) $3,100.00 (US guided)
#2					$3,750.00 (CT guided) $3,100.00 (US guided)
#3					$3,750.00 (CT guided) $3,100.00 (US guided)

I confirm that these patients are registered to the protocol referenced above, the patient numbers and procedure dates are correct, and the biopsies were performed for the purposes of the trial only, and that the biopsy was NOT standard of care and was NOT billed to insurance or the patient.

Signature: _____ **Date:** _____

If there are problems with this invoice, please contact:			
Name	**Phone**	**Fax**	**Email**

ECOG-Operations Office Use Only: TST Reviewer: _____
Date: _____

Patient	**#1**	**#2**	**#3**
Date of Registration to Step 1			
Registering Institution			
Data in STS indicates "Not billed to insurance"	☐	☐	☐
Sample indicated as received by the receiving laboratory in STS	☐	☐	☐
Approved	☐	☐	☐

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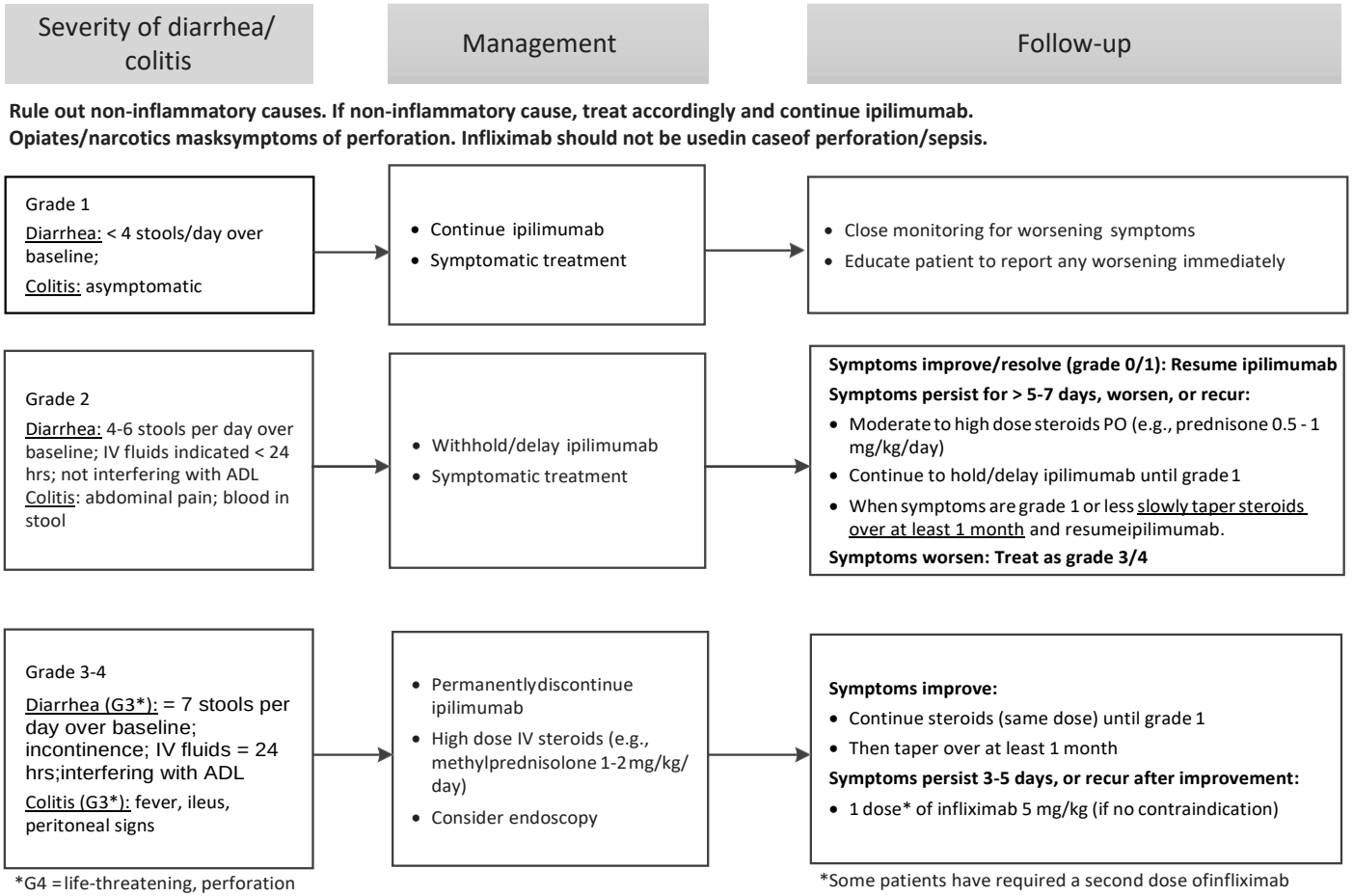
Appendix VIII
Ipilimumab GI Toxicity Management Algorithm (For Arms NOT administering Nivolumab: A, B, C, and Z only)



Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose at start of tapering or earlier , once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of PO Cortic osteroids.

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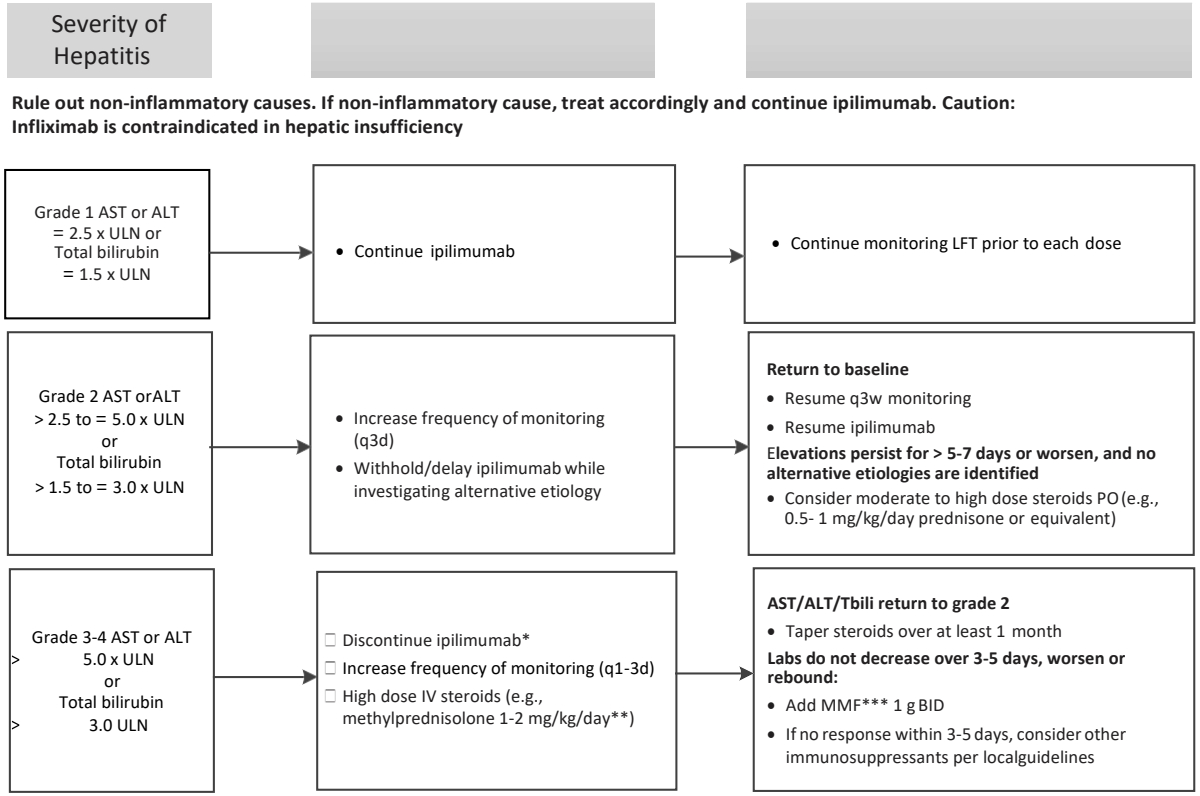
Appendix IX
Ipilimumab Hepatotoxicity Management Algorithm (For Arms NOT administering Nivolumab: A, B, C, and Z only)



* Ipilimumab may be held/delayed rather than discontinued if AST/ALT = 8 x ULN and Tbili = 5 x ULN. Resume ipilimumab when AST/ALT/Tbili return to grade 2 and meet protocol specific retreatment criteria.

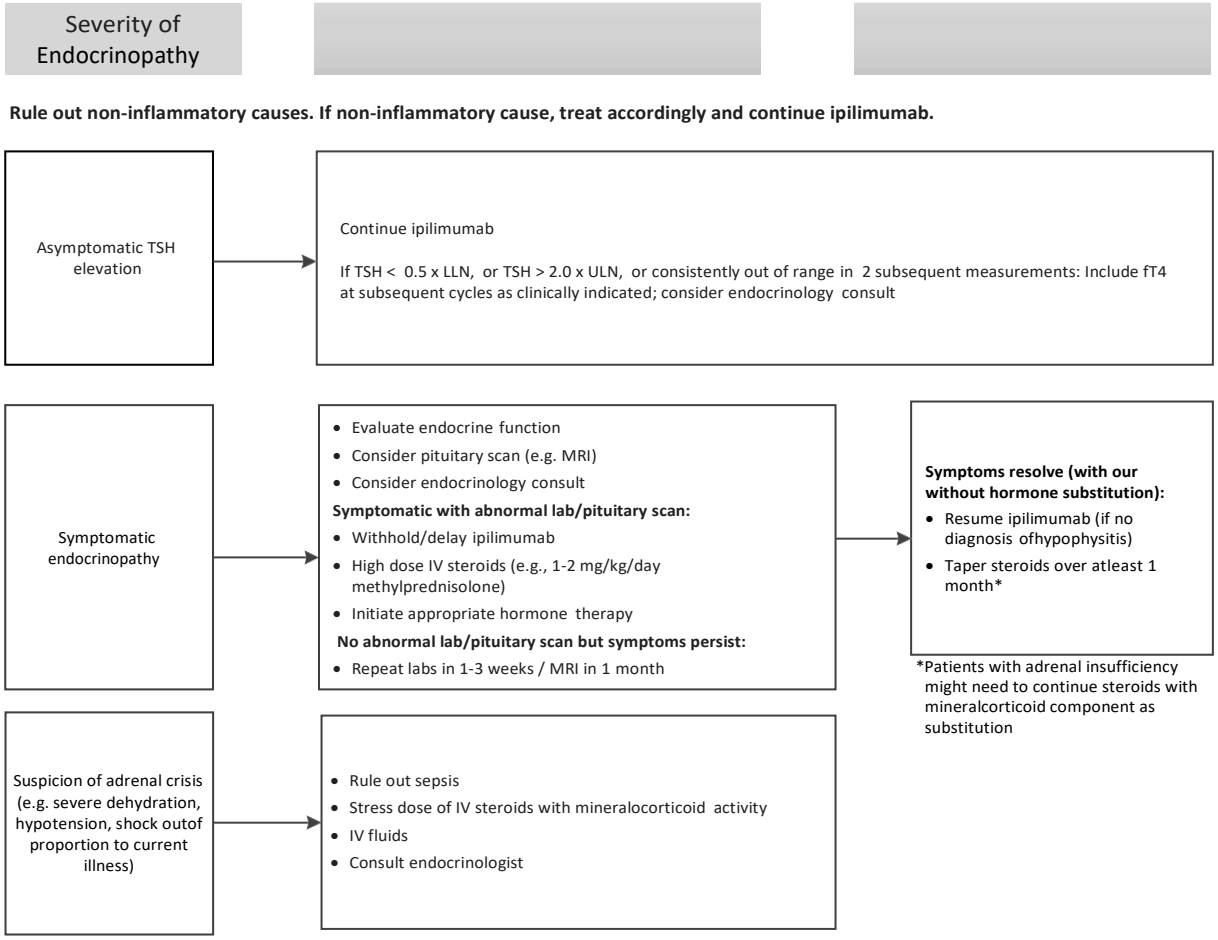
** The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

***MMF, mycophenolate mofetil

Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose at start of tapering or earlier , once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of PO corticosteroids.

A Phase I Study with an Expansion Cohort/Randomized Phase II Study of the Combinations of Ipilimumab, Nivolumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma

Appendix X
Ipilimumab Endocrinopathy Management Algorithm (For Arms NOT administering Nivolumab: A, B, C, and Z only)



Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose at start of tapering or earlier , once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of PO corticosteroids.

A Phase I Study with an Expansion Cohort/Randomized Phase II Study of the Combinations of Ipilimumab, Nivolumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma

Rev. 1/15

Appendix XI
Ipilimumab Skin Toxicity Management Algorithm (For Arms NOT administering Nivolumab: A, B, C, and Z only)

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue ipilimumab.

Severity of Skin Toxicity	Management	Follow-up
Grade 1-2	• Symptomatic therapy, e.g. antihistamines, topical steroids • Continue ipilimumab	**Symptoms resolve: Continue ipilimumab** **Symptoms persist > 1-2 weeks or recur with topical corticosteroids:** • Moderate to high dose steroids PO (e.g., prednisone 0.5 - 1 mg/kg/day) • Once controlled, taper steroids over at least 1 month
Grade 3-4	• Hold/delay ipilimumab (regardless of relationship) • Take photos of rash • Consider skinbiopsy • Dermatologyconsult • High dose IV steroids (e.g., methylprednisolone 1-2mg/kg/day)	**Symptoms resolve / return to grade 1:** • Taper steroids over at least 1 month • Resume ipilimumab if grade 3 • Discontinue if grade 4 toxicity considered related

Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose at start of tapering or earlier , once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of PO cortic osteroids.

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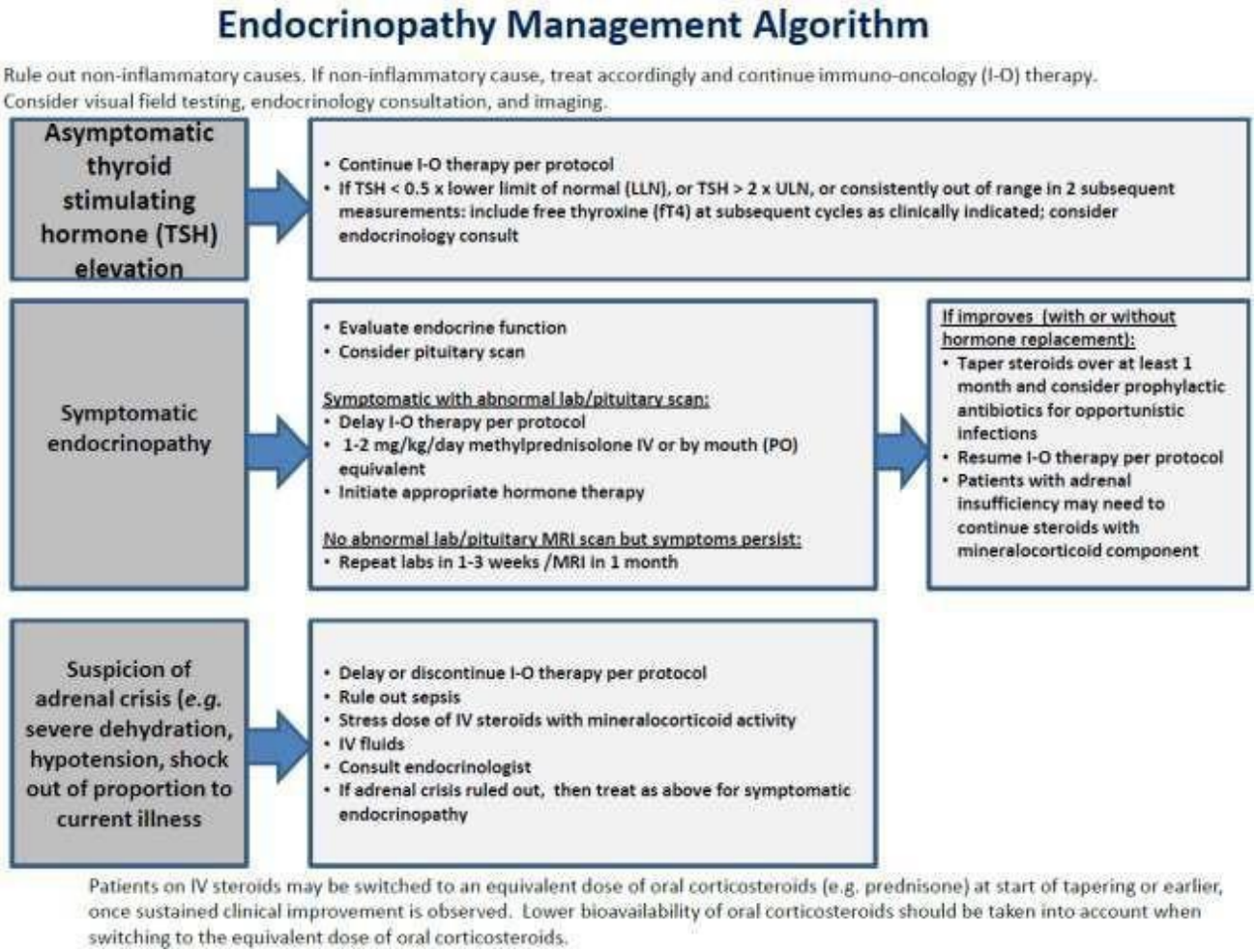
Appendix XII
Nivolumab Endocrinopathy Adverse Event Management Algorithm (For all Arms Administering Nivolumab: D, E, F, G, H, I, X, Y, K, and L only)



A Phase I Study with an Expansion Cohort/Randomized Phase II Study of the Combinations of Ipilimumab, Nivolumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma

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Appendix XIII
Nivolumab GI Adverse Event Management Algorithm (For all Arms Administering Nivolumab: D, E, F, G, H, I, X, Y, K, and L only)

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade (G) 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hours (hrs); not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with activities of daily living (ADL) Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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Appendix XIV

Rev. 9/15, Add16

Nivolumab Hepatic Adverse Event Management Algorithm (For all Arms Administering Nivolumab: Arms D, E, F, G, H, I, X, Y, K, and L only)

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin (T. bili) > ULN - 1.5 x ULN	• Continue I-O therapy per protocol	• Continue liver function tests (LFT) monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN and /or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 gram (g) twice daily (BID) • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**

****The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.**

A Phase I Study with an Expansion Cohort/Randomized Phase II Study of the Combinations of Ipilimumab, Nivolumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma

Appendix XV

Rev. 9/15, Add16

Nivolumab Neurologic Adverse Event Management Algorithm (For all Arms Administering Nivolumab: Arms D, E, F, G, H, I, X, Y, K, and L only)

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

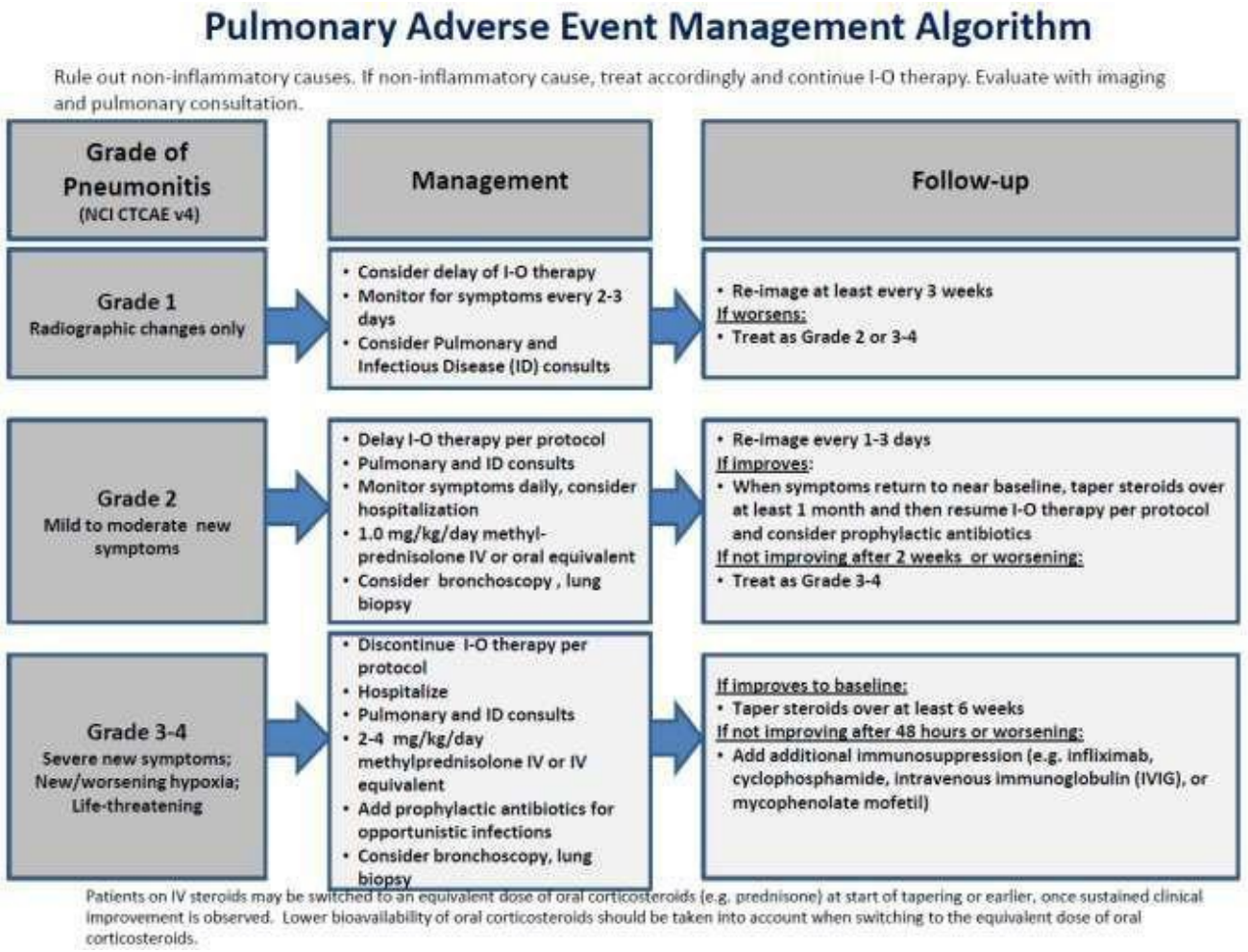
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

A Phase I Study with an Expansion Cohort/Randomized Phase II Study of the Combinations of Ipilimumab, Nivolumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma

Appendix XVI

Rev. 9/15, Add16

Pulmonary Adverse Event Management Algorithm (For all Arms Administering Nivolumab: Arms D, E, F, G, H, I, X, Y, K, and L only)



A Phase I Study with an Expansion Cohort/Randomized Phase II Study of the Combinations of Ipilimumab, Nivolumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma

Appendix XVII

Rev. 9/15, Add16

Renal Adverse Event Management Algorithm (For all Arms Administering Nivolumab: D, E, F, G, H, I, X, Y, K, and L only)

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > upper limit of normal (ULN) and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	If returns to baseline: •Resume routine creatinine monitoring per protocol If worsens: •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy	If returns to Grade 1: •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol If elevations persist > 7 days or worsen: •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	If returns to Grade 1 : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

A Phase I Study with an Expansion Cohort/Randomized Phase II Study of the Combinations of Ipilimumab, Nivolumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma

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Appendix XVIII
Skin Adverse Event Management Algorithm (For all Arms Administering Nivolumab: D, E, F, G, H, I, X, Y, K, and L only)

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Rash (NCI CTCAE v4)	Management	Follow-up
Grade 1-2 Covering ≤ 30% body surface area (BSA)*	• Symptomatic therapy (e.g. antihistamines, topical steroids) • Continue I-O therapy per protocol	<u>If persists > 1-2 weeks or recurs:</u> • Consider skin biopsy • Delay I-O therapy per protocol • Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving , taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol <u>If worsens:</u> • Treat as Grade 3-4
Grade 3-4 Covering >30% BSA; Life threatening consequences*	• Delay or discontinue I-O therapy per protocol • Consider skin biopsy • Dermatology consult • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent	<u>If improves to Grade 1:</u> • Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

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Appendix XIX

What to do if a patient comes in with possible immunotherapy-induced Myocarditis?

Javid Moslehi and Doug Johnson (Vanderbilt)

Detection:

Troponin – screening per Section 7

If troponin elevated, then obtain diagnostic workup, including:

Clinical examination for signs of heart failure, ischemia, arrhythmia and skeletal muscle myositis.

EKG, to rule out myocardial ischemia

For myocarditis, special attention to heart block, PR prolongation, QRS duration

CK (for concomitant myositis), CK-MB

Assess cardiac function via cardiac imaging

Echo (structural heart disease)

Consider cardiac MRI if available

Monitoring

If troponin elevated but not symptomatic and no arrhythmia, then hold immunotherapy and obtain troponin every 2-3 days with concurrent CK, CK-MB, and EKG until normalized. If normalized within 2 weeks, may proceed with treatment otherwise hold further therapy.

If troponin elevated and patient symptomatic and/or suspected myocarditis, admit to the hospital:

Monitor troponin, CK, CK-MB

Continuous cardiac monitoring

EKG at least daily

Cardiology consult

If other cardiac causes for patient's symptoms are ruled out, and the most likely diagnosis is myocarditis, a myocardial biopsy is strongly encouraged to confirm immune mediated myocarditis. Cardiac MRI may be an alternative to myocardial biopsy for diagnosis.

Treatment of presumed or confirmed myocarditis

Early cardiology consultation is strongly encouraged. Since most cardiologists are unaware of immune related adverse events, cardiology education about the therapies and adverse effects is important. Particularly, since EKG manifestations (specifically, heart block) appear to be an early manifestation of this entity, would favor consideration for pacemaker placement.

The optimal approach for treatment of myocarditis has not been established. Since this toxicity has caused patient deaths aggressive management is encouraged. Corticosteroids (see below) may be started while pending definitive diagnosis, if myocarditis is suspected.

Methylprednisolone 2mg/kg IV daily

Alternatively, methylprednisolone 1g daily (dose used for acute allograft rejection in cardiac transplantation) could be considered.

Based on the experience with other immune-related adverse events and cellular-mediated cardiac transplantation, other agents to consider include:

Infliximab

Anti-thymocyte globulin (ATG)

Mycophenolate mofetil

Tacrolimus

Investigational Studies

Defining mechanisms of toxicity is the best means to develop preventative and treatment strategies for immune mediated myocarditis.

If myocardial biopsy is obtained, then should get the following:

Formalin-fixed tissue (routinely done)

Frozen tissue (or snap frozen tissue)

In case of patient death, an autopsy can be helpful to help future cases

Education in terms of getting autopsy

Make sure whole set of organs is autopsied: skeletal muscle, endocrine (pituitary), liver, kidney

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Appendix XX

Rev. Add16

E4412 Stool Collection and Shipping Kit Order Instructions

Rev. Add19
Rev. Add20

NOTE: Blood collection kits are ordered as outlined in Section 11.3.1.

Stool specimen Collection/Shipping Kits are being provided by CENETRON CENTRAL LABORATORIES and are to be ordered ONLINE.

Starter kits are not available. It is preferred that baseline kit requests are made after patient consent, at a minimum the patient must be considered a candidate for consent and randomization.

Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000.

Ordering Process:

- At time of patient randomization, provide the contact for kit ordering in OPEN
- Following randomization of the patient to the trial, go to the website www.cenetron.com and click on the 'Order Kits' button at the top right. It is recommended that kits be ordered same day as patient randomization.
- The order form is not study specific and can be used for any study. Complete the online form as follows:
  - Sponsor (REQUIRED): ECOG-ACRIN
  - Contact Name (REQUIRED): Name of the institution kit contact. Should match the name of the individual provided in OPEN as the kit contact
  - Protocol Number (REQUIRED): E4412
  - Phone Number (REQUIRED): Phone number of the kit contact. Please ensure that this is a number that can be reached from an external caller
  - FAX Number: Fax number of the kit contact
  - Investigator: Last name of the kit contact is adequate
  - Email (REQUIRED): Email of the institution kit contact. Must be entered twice to confirm
  - Date Supplies Needed (REQUIRED): Add three (3) business days or more to order date. (E.g. if ordering on 2/5/2016, indicate 2/10/2016 to accommodate the weekend. Reminder that holidays must also be considered in this timeline)
  - KIT NAME (REQUIRED): Type in the kit type needed
    - E4412 Stool Collection Kit
  - Quantity: 1
  - Comments: Provide E4412 Patient Case ID# and full shipping address
    - Patient Case ID =' #####
    - *'Ship Kit to'* name of the individual to whom the kit is being shipped. (Maybe different than the kit contact provided above)
    - Full street address, town, state and zip code
  - Answer the security question

Please complete this form correctly, including the valid ECOG-ACRIN patient case number and complete shipping address. If information is missing the kit processing will be delayed.

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Appendix XXI

Biomarkers to Predict Toxicity of Immune Checkpoint Inhibitors

The following study was submitted and approved in response to the request for applications (RFA) for Administrative Supplements to Support Biomarker Studies Associated with NCI-supported Clinical Trials of Immunotherapy. The applications were administratively reviewed internally by NCI and reviewed and approved by DCTD/CTEP Protocol Review Committee separate from a protocol amendment

This study is utilizing specimens collected during the Phase I aspects of E4412.

Specific Aims:

Amidst the widespread enthusiasm greeting the therapeutic breakthrough of cancer immunotherapy, a key consideration has received relatively little attention: Toxicity. Although most patients tolerate these regimens well, a minority experience immune-related adverse events.

These events are *unpredictable, possibly severe, and potentially irreversible.* They may affect diverse organ systems. With combination immune checkpoint inhibitor therapy—which appears even more effective than single-agent therapy—up to 40% of patients may experience clinically significant immune-related adverse events.

We have developed a multi-faceted platform to develop predictive and pharmacodynamic biomarkers for immune-related adverse events. These assays include (a) autoantibody profiling, (b) HLA regulation and characterization, and (c) B- and T-cell receptor sequencing. These biomarkers are primed for clinical validation because we have already established accuracy, precision, analytical sensitivity and specificity, the reportable result range, reference intervals, reproducibility, and quality control in other populations (individuals with autoimmune disease and healthy controls). The proposed biomarkers are highly feasible because the bio-specimen requirement is minimal and no tissue is required. Our work is amenable to cross-trial and cross-network collaboration because our research focus is neither disease- nor therapy-specific.

Aim 1. Validate predictive and pharmacodynamic biomarkers for immune-related adverse events. *Aim 1a* Determine baseline and dynamic autoantibody profiles associated with immune-related adverse events using an array panel of 138 antigens including nuclear, cytosolic, and tissue-specific antigens (based on modifications to the validated Super-Panel and Antigen Panel 4). *Aim 1b* Determine HLA variants and determinants (more than 180 confirmed risk loci for autoimmunity) associated with immune-related adverse events. *Aim 1c* Determine patterns in T- and B-cell receptor repertoires associated with immune-related adverse events. **Total bio-specimen requirement** is (1) 100 µL plasma [autoantibodies] and *(2)* up to 7 µg PBMC DNA [1 µg HLA; 6 µg B-cell receptor, T-cell receptor]. *No fresh specimens or tissue are required.*

Aim 2. Integrate and analyze biomarker data and associated clinical data within and across trials. Our statistical/informatics team brings experience in the development of cross-trial analyses of large data sets (e.g., Lung Cancer Explorer; https://qbrc.swmed.edu/projects/lungcancer/). Clinical data (focusing on patient characteristics, treatment administered, and timing/nature/grade of toxicities) will be provided by ECOG-

ACRIN. We will develop systems for collection and analysis of data from the E4412 clinical trial that will permit subsequent integration with bio-specimen and clinical data from other clinical trials and biomarker assays.

Hypothesis:

We hypothesize that checkpoint therapy immune-related adverse events often result from the activation of pre-existing autoimmunity.

We are repurposing established methods in autoimmune diseases to the timely context of cancer immunotherapy. Our aims will provide unprecedented insight into predictors and mechanisms of autoimmune toxicities among patients receiving cancer immunotherapy. As these therapies are approved for more diseases, in more toxic combinations, and for earlier-stage cancers, a deeper understanding of these events will be critical.

Background and Significance:

The emergence of cancer immunotherapy has introduced an entirely new set of unpredictable, potentially severe, and possibly permanent toxicities. Immune checkpoint inhibitors targeting the cytotoxic T lymphocyte antigen 4 (CTLA4) and programmed death 1 (PD1) axes are transforming cancer treatment, with impressive clinical activity already leading to approvals for melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma, and bladder cancer. However, cancer immunotherapies also pose a risk for immune-related adverse events (irAEs). *These diverse toxicities are entirely distinct from the toxicities oncologists have come to expect with conventional chemotherapy and molecularly targeted therapies.*

Immune-mediated toxicities may impact almost every organ system, including brain, pituitary, thyroid, ocular, pulmonary, hepatic, intestinal, dermatologic, and adrenal.1 In contrast to the well- characterized temporal patterns of classic chemotherapy toxicities such as alopecia, nausea/vomiting, and myelosuppression, the onset and duration of irAEs remains unpredictable. Recent studies indicate that up to 80% of individuals receiving checkpoint therapies experience some form of irAE, with about 35% of all patients requiring systemic corticosteroid treatments to mitigate these events, and up to 20% terminating their therapy due to irAEs.2 These adverse responses convey substantial morbidity, incur considerable costs, and in some cases may preclude further use of these drugs. As immunotherapy use expands from major centers where pivotal trials have been conducted to smaller, isolated, and less experienced community sites, the ability to recognize and treat irAEs promptly may be challenged. With the FDA approval of combination PD1 and CLTA4 inhibition for melanoma in October 2015 and such combinations currently under study in other diseases, rates and severity of irAEs may be even greater in the future. ***To date, no clinical, laboratory, or radiographic biomarkers can predict these toxicities.***

The CTLA4 and PD1-PDL1 axes normally function to activate regulatory pathways that maintain peripheral tolerance to self-antigens.3 The therapeutic benefit of inhibiting these regulatory systems is thought to result from the amplification of suppressed anti-tumor immune responses that are blocked by tumor-specific manipulations of the immune system.4 However, these regulatory pathways are also intimately involved in the regulation of autoimmune and auto-aggressive immune responses.5 As a result, it is quite likely that any extant autoimmune responses that are being regulated by these peripheral pathways might also become activated during checkpoint blockade therapy.

Autoimmune disease, in which the recognition of self-antigens by the immune system leads to severe damage to specific self-tissues, is estimated to affect almost 10% of the U.S. population.6 Our recent SEER-Medicare analysis suggests that the prevalence of these

conditions may be even higher among individuals with cancer.7 Moreover, recent studies by our group and others have found that ***more than 26% of healthy individuals have strong IgG humoral immune responses to a variety of self-antigens,*** indicating that "benign" autoimmunity is much more common than autoimmune disease (**Figure 1**).8-11 These findings indicate that many healthy individuals exhibit significant autoimmunity that is regulated in the peripheral immune system by pathways such as those triggered by CTLA-4 and PD1. Consistent with this observation, CTLA-4 and PD1 are both known to potentiate autoimmune disease, suggesting that the inhibition of these regulatory pathways aggravates pre-existing autoimmunity.12-14 Based on this observation, **we hypothesize that checkpoint therapy irAEs often result from the activation of pre-existing autoimmunity.** We propose to test this hypothesis by utilizing a variety of novel technologies developed in the Department of Immunology at UT Southwestern to quantify autoimmune responses.

Research Approach:

***Aim 1*. Validate predictive and pharmacodynamic biomarkers-related adverse events.**

Bio-specimen Sources:

Bio-specimens (stored plasma and PRBCs) will be obtained from the E4412 trial. *This trial provides an optimal setting for the proposed toxicity- focused analyses* because they include multiple immune therapies, and (2) are anticipated to include prolonged treatment duration. The ECOG-ACRIN E4412 Study Chair and associated Committee Chairs have agreed to participate in this proposal. Our proposal has been reviewed and approved by the ECOG-ACRIN Laboratory Science and Pathology Review Committee (LSPRC). We have reviewed our specific bio-specimen requirements with the LSPRC and the E4412 Study Chair.

Feasibility:

Our proposed analyses are highly feasible and unlikely to interfere with other planned NCI supplement investigations for the following reasons:

Bio-specimen requirements are minimal and straightforward: (1) approximately 100 µL plasma for auto-antibody profiling, and (2) up to 7 µg DNA (from PBMCs) for HLA (1 µg DNA) and T/B cell receptor (6 µg DNA) characterization. There is no tumor tissue requirement, and all specimens may be stored.

We have demonstrated the ability to conduct all proposed laboratory and data analyses.

Few immunotherapy biomarker studies have focused on toxicity endpoints.

Our proposal may be adapted to optimize interactions with other projects: as the RFA encourages collaboration among funded proposals, our proposed aims may be modified to maximize the scientific yield of the RFA. Modifications could include expansion or removal of aims, inclusion of other bio-specimens and clinical data, examination of efficacy endpoints, and others.

Aim 1b. **Determine HLA variants and determinants (more than 180 confirmed risk loci for autoimmunity) associated with immune-related adverse events.** Genomic DNA from patient PBMCs will be genotyped in the Microarray Core using the Illumina Immunochip V2, which contains more than 250K SNPs for high density fine mapping of more than 200 immunologic loci. This will allow the following: 1) Principal component analysis of ancestry; 2) imputation of HLA class I and class II genotypes; and 3) genotypes for >186 confirmed risk loci for autoimmunity, including CTLA-4 and PD-1. HLA genotypes of particular interest include those with previously documented associations with autoimmune disease: HLA-DR3 (systemic

lupus erythematosis), HLA-DR5 (scleroderma), HLA- DR4/DR2 (mixed connective tissue disease), HLA-DRB (rheumatoid arthritis).

Aim 1c. **Determine patterns in T- and B-cell receptor repertoires associated with immune-related adverse events.** Because immune checkpoint blockade works by reducing suppressive signals to T-cells, a critical component to monitoring an individual's response to these drugs is comprehensive characterization of the clonal composition of lymphocyte populations.

Figure 1. T-cell receptor analysis of human PBMC samples. Number of unique TCR sequences detected in human PBMCs pre- and post-radiation therapy in responder *(left)* and nonresponder *(right).*

Recent advances in sequencing technology have revolutionized the approach to characterizing lymphocyte populations by enabling deep sequencing of the T-cell receptor and B-cell receptor repertoires in a variety of settings.[19-21] This technology enables the enumeration and quantification of hundreds of thousands of B- and T cell clones in each specimen and allows specific clones to be tracked over the course of an evolving immune response, including elucidating the impact of checkpoint blockade on T cell populations.[22,23] Most studies applying this technology in cancer have focused on T cells,[24] but some have characterized B-cell receptor repertoires in cancer patients.[25-27] As the production of auto-reactive antibodies may be particularly relevant to immune-related adverse events, we propose to characterize both T- and B-cell repertoires. We have previously demonstrated the ability to conduct such analyses (see **Figure 1**).

Total genomic DNA will be isolated from specimens (PBMCs) using a DNAeasy Blood and Tissue kit (Qiagen, Valencia CA). DNA yield and quality are determined using Nano Drop 1000 (Thermo Scientific, Waltham, MA). All specimen processing will be handled in Dr. Nancy Monson's laboratory, which has significant experience with repertoire deep sequencing on clinical specimens. Targeted PCR will be conducted to amplify the rearranged IgH and TCRB genes. Resultant PCR product will be subjected to agarose gel electrophoresis. Right-sized bands will be excised and purified. Dr. Monson's well-established protocols will be used.[28,29] Purified PCR product will then be sequenced by SeqWright, which conducted all of the repertoire sequencing done in the development of MSPrecise.[28,29]

Aim 2**. Integrate and analyze biomarker data and associated clinical data within and across trials.**

Statistical analyses will be performed by Drs. Yang Xie and Lindsay Cowell, with collaborative input from ECOG-ACRIN statisticians. Data will be normalized and quantitative values will be incorporated into a database (see *Database and cross-study analysis*). Specific questions to be addressed in analysis are: (1) Are autoantibody profiles predictive of immune-related adverse events? (2) Do specimens taken following a therapeutic dose leading to an immune-related adverse event demonstrate reactivity to immune-related adverse event-relevant tissue antigens or increased autoantibodies? (3) Do HLA genotypes predict development of immune-related adverse events? (4) Do patient T- and B- cell receptor sequences predict development of immune-related adverse events? (5) What is the association between autoantibody profiles, HLA genotypes, and T- and B-cell receptor sequences?

We will use a multi-step framework for proteome microarray analysis using standard microarray bioinformatics tools, which includes the following pre-processing steps: (1) background subtraction and averaging of duplicated spots, (2) normalization of the signal intensity of each Ag using internal controls across all specimens, and (3) normalized signal intensity (NFI) for each Ag (Ab) will be completed for each Genepix Report file generated per specimen by the centralized UT Southwestern Microarray Core. An example of our analyses with this pipeline for a selection of autoimmune diseases is presented in **Figure 4,** which profiles IgG autoantibody clusters from four different sample groups using autoantigen microarrays.

		Alternative AUC				
		0.65	0.7	0.75	0.8	0.85
Null AUC	0.5	115	64	40	28	20
	0.55	255	112	62	39	27
	0.6	987	244	107	59	37
	0.65	---	921	226	99	54

Table 2. Sample size estimation per group for evaluating prediction performance. Null AUC refers to the Area Under Curve for each ROC under the null hypothesis, which represents the clinically meaningful prediction performance. Alternative AUC refers to AUC under alternative hypothesis, which represents the expected prediction performance for the new assays.

Analysis of repertoire sequencing data will be conducted by Dr. Cowell's team using the VDJServer repertoire analysis infrastructure they developed under NIAID-funded R01 AI097403. VDJServer, (www.vdjserver.org) runs on the high-performance computing resources at the Texas Advanced Computing Center (TACC), thus enabling processing of extremely large data sets.

Comprehensive bioinformatics analysis on each data set will include platform-specific processing, pre-processing (using VDJPipe[30]), germline alignment (using IgBlast[24,31,32]), and repertoire characterization.

Comparison of repertoires between patients according to development of toxicity will include assessing sequence sharing, comparison of repertoires on a feature-by-feature basis, and feature selection by supervised classification. We will account for multiple hypothesis testing.[33] Finally, we will apply **supervised classification techniques from machine learning to determine complex sets of repertoire features that accurately classify specimens according to the development of toxicity or not.**

Such patterns, if found, could serve as a biomarker predicting risk of toxicity. To accomplish this, we will represent the full set of features for each repertoire and determine which subset of features is distinguishing for a particular group. We will utilize both Support Vector Machines (SVM) and Penalized Logistic Regression (PLR) and compare the classification accuracy between the two methods, an approach we have previously implemented.[34] We will integrate all of the immunologic profiles from all studies for a joint analysis of autoimmunity, immune-related adverse events, and T cell activation status.

Outcome analysis. For categorical clinical outcomes (i.e., immune-related adverse events), the Chi- square test or Fisher's exact test will be used to assess (1) the association between autoimmune status prior to therapy initiation and clinical outcomes, (2) the association between acquisition of autoimmune status subsequent to therapy and clinical outcomes, and (3) the association between immunity to cancer antigens and clinical outcomes. Because immunologic characteristics, and autoimmune profiles and adverse events will be measured repeatedly over time, the ordinary independence assumption of observations does not hold. We plan to use two approaches (linear mixed model and generalized estimating equations) to model correlated measurements. Missing data will be handled using the generalized-EM algorithm.[35,36] Subgroup analysis and multivariable logistic or linear regression analysis will be conducted to assess variations in association by specific cancer type and specific immunotherapies. In addition to capturing clinical data in the form of recognized, graded, and attributed immune-related adverse

events, we will work with our ECOG-ACRIN colleagues to examine other data potentially relevant to immune-mediated toxicity (e.g., lab values, fatigue, etc.).

Sample size for prediction models. To calculate sample size requirement for evaluating the performance of prediction models for immune-related adverse events, we estimate receiver operating characteristic (ROC) curves of the prediction models based on asymptotic variances approach. **Table 2** provides the sample size requirements to achieve 80% statistical power and control type I error at 5% for different assumptions of prediction models. For the E4412 study, if more than 20 patients have immune-related adverse events, we will have 80% power to detect alternative AUC at 0.85 when null AUC is assumed to be 0.5.

Recognizing that the prevalence of irAEs may be lower, partnering with other NCI-supported trials and investigators may complement our effort.

Database and cross-study analysis. The investigators from this proposed project have extensive experience in developing advanced user-friendly databases, and have developed two comprehensive clinical and molecular profiling databases: (1) the Lung Cancer Explorer (LCE) database (https://qbrc.swmed.edu/projects/lungcancer/), funded by UT Lung SPORE (P50CA-70907); (2) the Kidney Cancer Explorer (KCE) database (https://qbrc.swmed.edu/projects/kidneyspore/index.php), funded by UT Southwestern Cancer Center and the newly funded Kidney SPORE project (anticipated start date July 2016). Using a similar strategy, we will develop a comprehensive database to integrate the clinical data and molecular profiling data collected by this proposed project. The database will have controlled access to genetics data and all patient data will be de-identified. Similar to the LCE and the KCE databases, we will use a MySQL database with a Java API and use SOAP to structure all returned data. This allows users to easily connect our database to their preferred computing environments (R, SAS, Excel, C, Java, Perl, etc.). We will implement in the database the following elements: (1) effective visualization tools to display the molecular profiles; (2) integrative analysis and systems biology analysis tools for different types of data; (3) meta-analysis methods for cross-study validation and combinations of multiple studies to facilitate reliable biological and clinical discoveries. We will calculate the integrative correlation scores[37,38] across different types of datasets for cross-study validation.

Investigators' Team. The investigator team is highly qualified to carry out the proposed research.

- **Program Director/Principal Investigator: David Gerber, MD,** is a thoracic medical oncologist with active research funding from the NCI, the DOD, and the Cancer Prevention and Research Institute of Texas. He is highly active in ECOG-ACRIN, where he serves on the thoracic core committee, is Study Chair of E4512, is UT Southwestern site PI, and PI of the associated U10 LAPS grant.
- **Clinical Investigator: Catherine Diefenbach, MD,** is Assistant Professor ofMedicine, NYU Perlmutter Cancer Center, and E4412 Study Chair.
- **Clinical Laboratorians: Quan Li, PhD,** is Associate Professor of Immunology and Internal Medicine. He is director of the Microarray Core facility at UT Southwestern and has extensive experience in autoantibody profiling. **Nancy Monson, PhD,** is Associate Professor of Immunology and Neurology. She has extensive experience with high-throughput repertoire sequencing on clinical specimens for T- and B-cell receptor profiling. **Ward Wakeland, PhD,** is Professor and Chair of the Department of Immunology at UT Southwestern and an expert in molecular characterization of autoimmune disease.
- **Statisticians/Informaticians/Computational Scientists: Lindsay Cowell, PhD,** brings knowledge and expertise in statistics, bioinformatics, and immunology. She has anNIAID-

funded project developing methods for the analysis of high-throughput immune repertoire sequencing data, and implementing open source software to make these methods widely available. **Yang Xie, MD PhD,** is director of the Quantitative Biomedical Research Center and the Bioinformatics Core Facility at UT Southwestern. Her methodological expertise is in developing rigorous statistical methods for high- throughput data analysis, Bayesian joint modeling, biomarker analysis, predictive modeling, and synthesis of large data sets including genomic and clinical data points.

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A Phase I Study with an Expansion Cohort/Randomized Phase II Study of the Combinations of Ipilimumab, Nivolumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma

Appendix XXII

Rev. Add20

Proposal of Correlative Studies in Collaboration with the CIMAC-CIDC Network

The following proposal was submitted and approved by CIMAC for use of Phase I specimens from E4412 patients who consented '*Yes*' to '*May we keep any samples leftover after the central review and laboratory research studies for research about cancer?*'

A. Lead CIMAC for the Project:

CIMAC PI and Institution: Sacha Gnjatic, Adeeb Rahman, Seunghee Kim-Schulze, Mount Sinai and Ignacio Wistuba, MD Anderson Cancer Center.

Contact Person: Sarah Fayle, Celia Garcia-Prieto

Summary of Biomarkers and Methodology: Proposed Biomarkers by Order of Priority

Priority	Biomarker Name	Assay (CLIA: Y/N)	Purpose	Sample Types and Time Points of Sample Collection		Mandatory or Optional?	Assay Lab	Already embedded in protocol?	Funding Source
1	CYTOF	(CLIA:N)	• Integrated • Correlation with response	PBMCs	3-4X (Baseline, Pre (D1C2), Restaging, off-study)	M	CIMAC- Mount Sinai (Adeeb Rahman)	N	CIMAC
2	Olink	(CLIA:N)	• Exploratory • Correlation with response	Plasma	3-4X (Baseline, Pre (D1C2), Restaging, off-study)	M	CIMAC- Mount Sinai (Seunghee Kim-Schulze)	N	CIMAC
3	Grand Serology	ELISA (CLIA: N)	• Exploratory • Correlation with response	Plasma	3-4X (Baseline, Pre (D1C2), Restaging, off-study)	M	CIMAC- Mount Sinai (Sacha Gnjatic)	N	CIMAC

Priority	Biomarker Name	Assay (CLIA: Y/N)	Purpose	Sample Types and Time Points of Sample Collection		Mandatory or Optional?	Assay Lab	Already embedded in protocol?	Funding Source
4	TCRseq	Immuno-seq (CLIA: N)	• Exploratory • Correlation with response and with TCR sequences in tumor	PBMCs	3-4X (Baseline, Pre (D1C2), Restaging, off-study)	O	CIMAC- Mount Sinai (Seunghee Kim-Schulze) and Adaptive Biotech	N	CIMAC

Summary of Requested Samples and Availability: Specimen Availability for CIMAC Assays (Phase I Only)

Bio-specimen Types Requested	Where Specimens will be Banked	Time Points of Specimen Collection	Number of Cases Collected on the Trial	Number of Cases Requested for CIMAC	Quantity of Specimens Requested for CIMAC per Case	Purpose	Number of Cases with Available Biospecimens
PBMC	Transfer aliquots from EA CBPF to MS-CIMAC	3x: Baseline C2Week9 Progression	See last column	All patients available	1 vial at min. 10e6 cells/vial	CyTOF	There are 58 of 62 patients that have submitted at least one timepoint of PBMCs and serum, and 54 of these have baseline samples. There are > 40 patients who have at least 2 timepoints. One pre-treatment and one interim timepoint will be analyzed for each patient. For each patient, there are multiple vials of PBMCs and serum stored. For the purposes of this analysis we will use 1 vial of PBMC and one vial of serum from each timepoint.
Plasma	As above	3x: Baseline C2Week9 Progression	See above	All patients available	1 vial for each time point	Olink	See above

Bio-specimen Types Requested	Where Specimens will be Banked	Time Points of Specimen Collection	Number of Cases Collected on the Trial	Number of Cases Requested for CIMAC	Quantity of Specimens Requested for CIMAC per Case	Purpose	Number of Cases with Available Biospecimens
Plasma	As above	3x: Baseline C2Week9 Progression	See above	All patients available	Same vial as above for each time point	ELISA Grand Serology	See above. The same vial will be used for Olink and ELISA/Grand Serology

Specimens for Non-CIMAC Assays

Biospecimen Types	Time Points of Sample Collection	Specimens	Quantities Used	Purpose
Plasma	Baseline	Plasma	1 vial each. Enough remaining for MS-CIMAC proposed assays.	A collaboration with David Gerber at UT Southwestern is ongoing to look at serum markers of autoimmune toxicity of checkpoint inhibitor therapy. The specimens used will not preclude analyses planned for CIMAC, as there should be sufficient serum banked and remaining from each patient and time point. The data generated may be able to be shared and integrated after publication, in collaboration with Dr. Gerber.

B. Biomarker Objectives and Scientific Hypothesis:

The currently proposed exploratory biomarkers are to:

1) Composition of peripheral blood cell subsets and their surface markers measured by high-dimensional CYTOF mass cytometry (such as stimulatory or inhibitoryreceptors, memory/naïve markers…) are differentially affected by treatment and by clinical outcome.
2) Changes in soluble analytes such as cytokines, chemokines, and other proteins shed by tumors or immune cells, measured using Olink, are related to treatment and could be linked to clinical endpoints.
3) Induction of spontaneous humoral immune responses to a series of known tumor antigens, as measured by ELISA Grand Serology, and how titers may be affected (induced, reduced, increased, lost) by treatment. Association with clinical endpoints will be tested as well.

C. Background and Study Justification:

The tumor biology of Hodgkin Lymphoma (HL) is unique, consisting of a malignant Hodgkin Reed-Sternberg (HRS) cells which comprise a small fraction (0.1–10%) of the total cellular population. Immunostains are characteristically positive for CD15 and CD30, and this pattern confirms diagnosis. These HRS cells reside in a milieu of reactive inflammatory cells that create an inflammatory microenvironment supportive of tumor growth[2-5]. HRS cells orchestrate their microenvironment to avoid immune attack by suppressing anti-tumor immune surveillance[6].

Brentuximab vedotin (BV), an antibody drug conjugate (ADC) directed against CD307 conjugated to an anti-microtubule drug, monomethyl auristatin E, received accelerated approval by FDA in 2011 for the treatment of HL relapsed after ASCT or after 2 lines of chemotherapy and ineligible for ASCT. In a pivotal phase II study, 102 patients with relapsed or refractory HL after ASCT, who received a median of 3.5 prior therapies, were treated with 1.8mg/kg BV every 3 weeks for maximum of 16 cycles with ORR of 75%, including CR 34%. The median duration of response (DOR) was 6.7 months for responders and 20.5 months for complete responders, with PFS of 5.6 months in the whole group and

up to 21.7 months in complete responders8. This low CR rate and short PFS rate, was part of the initial rationale for combining BV with checkpoint inhibitor therapy in E4412.

In 2016 the checkpoint inhibitor nivolumab (N) obtained accelerated approval by the FDA for HL that has relapsed or progressed after ASCT and post-transplantation BV. In a phase I study of single agent nivolumab which treated 23 patients with relapsed or refractory HL toxicity was manageable, and the activity was extremely high with an ORR of 87%, including 17% CRs, and PFS at 23 weeks of 86% [9]. The drug was well tolerated without significant DLTs. Immunohistochemistry confirmed the high level of PD-L1 expression in HRS cells in this study. As updated at ASH in 2016, after an extended follow up of 101 weeks, the median duration of response and median PFS were reached at approximately 13.1 months and 14.8 months respectively demonstrating long responses, but suggesting that ultimately relapses are occurring on single agent checkpoint inhibitor therapy. Thus, although highly active Nivolumab alone may be inadequate for long term disease in this traditionally difficult to treat patient population (ASH annual meeting 2016). Again, durability was higher for patients achieving CRs, but only 8% of patients achieved CRs.

Preclinically, drug conjugates such as CD30 BV have been shown on their own to have immunomodulatory properties via stimulation of dendritic cells[10]. Ipilimumab and nivolumab have been extensively investigated for a variety of changes in T cells and myeloid cells in the periphery. Up-regulation of the receptor programmed death ligand-1 (PDL-1) on HRS cells induces anergy in peritumoral T cells (19, 20). The T cell exhaustion and deficient anti-tumor immunity induced by the HRS cells within their microenvironment play a key role in creating and propagating a permissive milieu for HL growth. This mechanism is also key to the clinical efficacy of nivolumab.

The HRS cells themselves appear to play a key role in suppressing the cytotoxic activity of the T cells in the tumor microenvironment. The HRS cells secrete cytokines such as Tarc (CCL17), CCL5, and CCL22 attracting Th2 and Treg cells, and the interleukin IL-7, which induces differentiation of naïve CD4+ T cells towards FoxP3+ Treg cells[11-14]. These can be easily measured and followed during treatment as biomarkers of drug activity.

T cells are the most abundant cells in the HL microenvironment[15] and are dysfunctional, appearing anergic even to recall antigens when stimulated[16]. This can be alleviated in vitro with anti-CTLA-4. The rationale is that adding checkpoint blockade to a tumor targeting drug may overcome the suppressive microenvironment and lead to induction of a functionally distinct active immune subset. CYTOF is a good method to comprehensively characterize dysfunctional immune cells in HL[17].

We will therefore test the hypotheses that CD30 BV when combined with checkpoint blockade induces maturation of DC, activation and re-polarization of CD4 T helper cells, reduction of exhaustion markers and Tregs, increase in proinflammatory cytokines, and that dual checkpoint blockade will synergize these effects due to non-overlapping immunomodulatory properties.

No CD30 testing is required for eligibility as all patients with HL are expected to express the molecule, which is the target of the tumor-targeting component of the combination immunotherapy.

This is why we chose the following biomarkers: CYTOF to assess comprehensively changes in phenotypic and functional immune subsets occurring in each arm, Olink to measure proinflammatory serum analytes, ELISA/Grand Serology to assess changes in immunogenicity to known HL-expressed tumor antigens, and TCRseq to monitor clonality and diversity evolution with treatment, as a surrogate of T cell specific changes.

CYTOF:

We will use all available time points for the biomarkers proposed: baseline, during treatment when peak changes are expected, and in patients who progress, at time of progression. The largest changes based on previous experience with CYTOF are expected from baseline to C2week9, though there is no prior experience comparing various cohorts and assessing the differential effect of ipilimumab vs. nivolumab vs. ipilimumab+nivolumab in this patient population also receiving anti-CD30 treatment. Statistical justifications are also taken into consideration based on expected changes in SD of specific markers or population of 10-30%. Though analyses will be agnostic and will query populations that show the greatest changes in each cohort compared to baseline regardless of cell type, we will pay particular attention to changes in ICOS, TIM3, LAG3, Tregs, memory T cells, and myeloid cell with potential suppressive activity based on findings from other multiple studies post-ipi and post-nivo using flow cytometry or CYTOF.

ELISA/Grand Serology and Olink:

Only few papers have investigated Hodgkin for expression of tumor antigens with immunogenic potential, and therefore possible targets of immunomodulation by the immunotherapy proposed. These include PRAME[18], WT1[19], and cancer-testis antigens in particular in resistant HL[20,21]. Our prior work in solid tumors shows increases in antibody titers from baseline to week 12 to NY-ESO-1 following ipilimumab treatment of metastatic melanoma patients (Yuan, Gnjatic, PNAS 2011), as well as preexisting titers showing correlation with clinical benefit. Prior experience with Olink in immuno-oncology is still limited but other soluble multiplex platforms have shown proteomic changes expected to be seen. We will analyze all 92 onco-immunology-related analytes from Olink, with particular interest in changes in IL-10 and IL-6 from pre-treatment.

TCRseq is also proposed as a metric of changes in T cell diversity and clonality, and emergence of preferred clones post-treatment. This optional assay is performed using a fraction of the PBMCs planned for CYTOF experiments that are then sent to Adaptive Biotech for their standard Immunoseq platform. Metrics will be compared across the three arms, to assess the differential role of each checkpoint inhibitor or their combination on peripheral T cell repertoires. While this assay on its own may have limited value given the low predicted frequency of tumor antigen-specific clones in circulation, it will show its full value once the same TCRseq analysis is applied to tumor samples as well, using FFPE. A portion of these locally infiltrating T cell receptors should have a higher degree of relevance to the tumor and in turn, can help interpret changes observed in the periphery.

We hypothesize that evidence of immune dysregulation and T cell anergy in the systemic circulation will serve as biomarkers of disease activity; the levels of these biomarkers will be elevated pre- treatment, will decline significantly during therapy in responders, and will be predictive of treatment response.

Results will be shared with PI through CIMAC and CIDC. Communicating results to patients is at the discretion of PI.

D. Statistical Considerations

1. Endpoints (Outcomes)

Correlations will be attempted with endpoints listed in primary and secondary objectives.

2. Statistical Analysis Plan for Biomarker Analysis:

MS-CIMAC has built an analytical pipeline for Olink and CYTOF based on Phenograph, Zinc, and Citrus algorithms that use either paired t tests for differences across longitudinal samples or linear regressions for cohort comparisons, together with multiple comparison corrections. These will be available as interactive tools to query changes in communities of cells detected with CYTOF based on dimensionality reduction algorithms viSNE, or for groups of clustering soluble analytes for O-link. Finally, along with these statistical plans and tools, an array of descriptive statistics will be provided to explore potential differences that have not been addressed in the current plan.

Changes in the value of the biomarkers from the methods above will be studied over time. Descriptive plotting of biomarker values for all patients with available data stratified by response status, survival- and progression-free survival status will be presented. We will use smoothing techniques to bring out the distinctive patterns as much as possible. PROC LOESS will be used for smoothing.

Below are statistical considerations from Madhu Mazumdar, PhD and Vivien Huang, MS, biostatisticians at MS-CIMAC.

Power:

This study initially aimed to enroll 65 patients with relapsed/refractory Hodgkin's lymphoma, who will receive treatment with the combinations of Ipilimumab, Nivolumab and Brentuximab Vedotin. The biomarkers were planned to be examined prior to the start of treatment, prior to cycle two, time of first restaging PET/CT, and after completion of therapy/off treatment. Our unit of analysis is patient and the endpoint used is the paired difference between biomarker values measured at two time points, before treatment, labelled as 'Pre' and after treatment, labelled as 'Post'. We assume an equal standard deviation (SD) at both pre- and post- assessments and compute the SD of paired differences.

At present, more than 40 patients provided at least two samples. Table 1 exhibits the minimum detectable paired differences under scenarios of SD pre/post at 10%, 20%, 30% for the sample size of 40 patients.

Sample Size	SD pre/post	SD of Paired Differences	Alpha	Power	Minimum Detectable Mean Paired Differences
40	10%	13.42%	0.05	0.8	6.1%
40	10%	4.47%	0.05	0.8	2.0%
40	20%	26.83%	0.05	0.8	12.2%
40	20%	8.94%	0.05	0.8	4.1%
40	30%	40.25%	0.05	0.8	18.3%
40	30%	13.42%	0.05	0.8	6.1%

A sample size of 40 with 5% level of significance and 80% power will be able to detect a mean of paired differences ranging from 2.0% to 18.3%. This calculation is based on a two-sided paired t-test and no multiple comparison adjustment is made. Power was calculated using software PASS 15.0.5.

As no previous research was available on which to base the correlation of repeated measures, power was computed with the paired t-test as opposed to the linear mixed

model (LMM) approach described in our analysis plan. Approximate standard deviation estimates were used.

Analysis Plan:

Descriptive statistics will be prepared to summarize the biomarker data. We will present means, standard deviations, and smooth plots for the measured values of individual biomarkers over time stratified by treatment and clinical response, respectively.

To evaluate the potential biomarker response targets monitored over time using Olink and Cytoff assays, a Mixed Model Analysis of Covariance (MMANCOVA) with a random intercept to account for correlation of repeated measures within a patient will be developed to assess the difference in mean biomarker values across all the time points1. All patients with at least one biomarker value (n=58) will be included in the model. Normality of the biomarker intensities will be examined and log-transformation to achieve normality will be performed as appropriate. Measurement time points (baseline and potentially three follow-up time points), treatment combinations (a total of three treatment combinations), and doses (a total of seven dose combination plans) will be included as fixed main effects together with an interaction term between time and treatment [2,3]. The main difference between treatment combinations at each follow-up time point will be estimated along with a 95% confidence interval using a linear combination of estimators in Proc Mixed. The correlation among repeated measures of biomarker intensities over time will be assumed to follow a linear exponent AR(1) ("LEAR") structure which covers the entire spectrum of rates of correlation decay between compound symmetry (no decay) and first-order autoregressive AR(1) (fast decay) by using a simple two-parameter specification4. The MMANCOVA model will be performed with each biomarker represented by the following equation which models the biomarker with all of the accountable sources of variance in the experiment:

$$Y_{ijkl} = \mu + \alpha_j + \beta_k + (\alpha\beta)_{jk} + \gamma_l + \pi_i + \epsilon_{ijkl}$$

i: patient, I = 1, …., 58

j: treatment combination, j = 1, 2, 3

k: time point, k = 1, 2, 3, 4

l: dose combinations, l= 1, 2, 3, 4, 5, 6, 7

where Y_{ijkl} is the biomarker value (or its transformation) for ith patient on jth treatment combination and lth dose at kth time point; μ is the mean value of the biomarker at baseline with the reference treatment at a reference dose; α_j is the deviation associated with jth treatment combination relative to the reference treatment; β_k is the deviation at kth time point relative to baseline; $(\alpha\beta)_{jk}$ is the interaction term between treatment combination and time point; γ_l the deviation associated with lth dose relative to the reference dose; $\pi_i \sim N(0, \sigma^2)$ represents the patient random effect; and ϵ_{ijkl} is the random error. The methods accounting for multiple comparisons, provided by the LSMESTIMATE statement in the PROC MIXED procedure, among the three treatment combinations will be used to decide the significance of the hypothesis test5. This model is flexible enough to accommodate additional variation sources, if any arise (e.g., due to patient covariates, multi-center characteristics, sources of specimen etc.) by modeling additional fixed and random effect terms. The analyses will be conducted using SAS 9.4 software.

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3. Statistical Considerations for Secondary Objectives

Description of Bioassays and Platforms for Proposed Biomarkers:

Analytical performance for CYTOF, Olink, and ELISA/Grand Serology performed at MS-CIMAC available as attachments.

Thanks to the 3-arm design of study E4412, the assays proposed below will allow to differentially examine the effect on immune responses for combination checkpoints vs. individual checkpoints, when co-administered with Brentixumab vedotin.

CYTOF Mass Cytometry Profiling:

High-dimensional single cell monitoring is a key strategy to elucidate complex phenotypic and functional characteristics of heterogeneous immune populations. This is a broadly applicable approach that can provide valuable insights into disease mechanisms and therapeutic responses and potentially identify correlative cellular biomarkers in the context of many different trials. Some of the key challenges in maximizing the impact of cellular immune monitoring are to increase the number of parameters that can be examined simultaneously in a single sample while minimizing experimental and technical variability. The MS-CIMAC has established a robust cytometric platform addressing both of these challenges using a CyTOF2 mass cytometer.

Mass cytometry[22] uses antibodies conjugated to rare-earth metals, resulting in cleaner, higher-dimensional data compared to conventional flow cytometry. With it, we can evaluate up to 55 independent parameters in a single sample, including over 40 antibodies against surface and intracellular targets, or nucleic acid labels to identify cells, assess their viability and evaluate cell cycle. We can also use barcoding reagents to enable pooled samples analysis to minimize experimental variability, improve sample throughput and reduce costs. Because of its sample-sparing nature, we propose to use CyTOF for phenotypic and functional analyses of PBMC as well as single cell suspensions of fresh tumors whenever available, with one million viable cells providing ample information.

The MS-CIMAC has invested heavily to establish a comprehensive CyTOF mass cytometry pipeline led by Dr. Rahman. It includes optimized sample processing SOPs, a

reagent bank of over 500 metal-conjugated antibodies, a range of curated immune profiling panels, custom antibody conjugation services, and an efficient data processing pipeline. As one of the most active clinically-focused mass cytometry programs in the country[23-44], we routinely apply high dimensional mass cytometry in a range of applications, including phenotypic characterization of rare clinical samples, functional studies of multiplexed intracellular cytokine detection and phosphoprotein detection.

Full analytical validation has been deposited as a document within the CIMAC network, and the following tables summarize the type of data collected and outputs, as well as an overview of the analytical variables considered.

Assay Type	Primary Assay Outputs	Pre-processing/ Normalization /QC	Initial Analyses	Derived Data Outputs
O-Link	92 parameter targeted soluble factor immunoassay	Normalized protein eXpression (NPX)	Multivariate coexpression analyses	Quantification and correlation of multiplexed cytokine levels

OLINK PROTEIN SOLUBLE ANALYTES	
(i) accuracy	Accuracy determined by replicate analysis of spiked in known amounts of analytes in multiple assays (described in Figure 2 of full analytical validation document).
(ii) precision: Inter-assay	Depending on the level of protein detected, % of CV varies such that 63 analytes with standard detection have a CV value of <10% and 16 analytes with low detection have a CV value <30%. Other analytes were not detected and CV was not calculated (see Figures 4, 9 and 10 in analytical validation document). Every Olink assay plate has “inter-plate control” wells to be used in monitoring the inter-assay variation and normalization of the data.
(iii) analytical sensitivity	For the lower limit of quantification (LLOQ) and upper limit of quantification (ULOQ), see Table 1 and Figure 3.
(iv) analytical specificity including interfering substances	Olink uses two monoclonal antibodies targeting two different epitopes of the target. (see Figure 5)
(vi) reference intervals (normal values) with controls and calibrators	Varies by analytes and sample matrices, i.e., plasma, serum, bone marrow aspirate, plasma etc.
(vii) standardization, harmonization, reproducibility and ruggedness	Assay standardization is established at levels of assay, operators and equipment, and Mt Sinai CIMAC has been recognized as a “Certified Service Provider of Olink Analysis” by the Olink company with strict training and following of SOPs. See Figures 1, 9, 10 and 11.
(viii) establishment of appropriate quality control and improvement procedures	MS-CIMAC measures inter- and intra-assay variations in regular intervals using in-house control samples (normal human plasma pooled from 15 subjects). MS-CIMAC was certified by Olink in June 2017 and the plan is to have annual refresher trainings by using Olink training kit.

OLINK PROTEIN SOLUBLE ANALYTES	
(ix) any other performance characteristics required for assay performance	All of the required equipment, including Biomark, Juno and PCR thermal cycler, have biannual preventive service contracts to maintain optimal performance. All other small equipment such as multi-channel pippetman also has biannual calibration performed by certified vendors.

ELISA/Grand Serology:

One approach to test whether tumors become more immunogenic as a result of immunotherapy is to measure naturally occurring antibodies to tumor antigens in patient serum or plasma. Autologous serotyping has resulted in a growing list of immunogenic human cancer antigens[45], including mutational, overexpressed, oncogenic viral, differentiation, and cancer-testis antigens. These antigens, though usually intracellular, reflect the immune system's capacity to detect abnormalities associated with neoplasia. The presence of antibodies to tumor antigens can be used as a marker of tumor presence or progression, but may also help generate T cell responses via immune complexes with cognate antigen. In some cases, such as the cancer/testis antigen NY-ESO-1, serum antibodies are associated with spontaneous T cell responses in peripheral blood. We propose to test the hypotheses that immunotherapy leads to induction or increase in immunity to locally expressed antigens by assessing serological changes pre-post treatment*, and that the serological repertoire in patients may be useful as a prognostic or predictive tool.*

We have shown that presence of baseline serum antibodies to NY-ESO-1 was correlated with clinical benefit to ipilimumab in metastatic melanoma patients[46], and that changes in NY-ESO-1 antibody titers also correlated with clinical events in a patient with abscopal response[47]. More generally, using serological markers as a surrogate for presence of antitumor immunity is proposed as a quick and affordable way to assess tumor immunocompetence and response.

We will perform an assay that we named **Grand Serology:** A series of known tumor antigens will be assessed in a hypothesis-driven manner for their capacity to elicit autoantibodies in treated patients. Using ELISA as previously described[48], we routinely test a series of 25 tumor antigens, including mutational, stem-cell, and cancer-testis antigens such as TP53, NY-ESO-1, SOX2, PRAME, WT1, MAGE-A3, SSX2, etc., most of which already have demonstrated immunogenicity in various solid and some hematologic tumors. Grand Serology is also ideally suited to test for potential for antigen spreading, i.e., development of seroreactivity to antigens unrelated to immunogens, which is a useful measurement to assess in immunotherapy. *We propose to use this assay systemically as a unifying measurement throughout all NCI-supported immunotherapy trials, to define baseline immunogenicity, quantify changes or induction in peripheral immunity with local or systemic treatments, and probe potential prognostic value.*

Full analytical validation has been deposited as a document within the CIMAC network, and the following tables summarize the type of data collected and outputs, as well as an overview of the analytical variables considered.

Assay Type	Primary Assay Outputs	Pre-processing/ Normalization /QC	Initial Analyses	Derived Data Outputs
ELISA and grand serology	Antigen-specific antibody titers	Check titration curves from internal controls, extrapolation based on internal controls	Normalized antibody titer after extrapolation.	Antigen specific antibody titers and fold change scores based on pre-determined cutoffs

ELISA GRAND SEROLOGY	
(i) accuracy	Determination of titration based on extrapolated curve, providing values with reproducible > 90% within a < 2x range.
(ii) precision	Ability to detect antigen specificity is dependent on format of antigen chosen (peptide, protein, denatured vs. native form). Nevertheless, high level of precision shown with comparing closely related antigens to irrelevant targets. Intra-assay and inter-assay CV calculated for NY-ESO-1 at 1.1% and 1.2% respectively. CVs are larger for titers near the limit of detection.
(iii) analytical sensitivity	Titers range from 1/1 (non significant) to greater than 1/1,000,000 and are dependent on number of dilutions tested.
(iv) analytical specificity including interfering substances	Specificity is determined by comparing reactivity to several antigens, including negative controls such as DHFR. Potential for “stickiness”, i.e., low-level titers (range 10-500) to a majority of antigens tested is observed in some samples, particularly after chemotherapy (possibly due to hemolysis in part). Procedures are in place in SOP to minimize this rare (< 5%) occurrence.
(vi) reference intervals (normal values) with controls and calibrators	Positive controls and expected OD ranges (< 300 for negative control sera at 1/100, > 1000 for positive controls sera at 1/100) and are specified in SOPs for each antigen tested in each plate.
(vii) standardization, harmonization, reproducibility and ruggedness	Assay was harmonized with Roswell Park, NordWest, and biotech company Serametrix, using reference specimens coordinated by the Gnjatic lab.
(viii) establishment of appropriate quality control and improvement procedures	Use of negative and positive serum control with known reactivity in each plate for each antigen, including healthy donor pools used as negative reference and known sera with reactivity as positive.
(ix) any other performance characteristics required for assay performance	Serum and plasma from either peripheral blood or bone marrow were found to be interchangeable for antibody titer determination. Urine and other fluids such as culture supernatants may be used but starting with undiluted material.

Remarkably few papers describe the capacity of Hodgkin Lymphomas to spontaneously elicit antibody responses to tumor antigens. Most antigen-specific work was done in the context of EBV- related HL. Presence of targets included in the Grand Serology panel, such as WT1 or PRAME, or cancer/testis antigens will therefore be of interest to not only describe their naturally occurring immunogenicity in this tumor type, but changes in titers observed with treatments that we intend to test for their titer occurrence and changes over time and across cohorts. In addition, not much is known of the immune

repertoire elicited by the specific population studied here of patients who have refractory advanced HL, and whose tumors are expected like other tumor types to have more aberrantly expressed tumor antigens associated with progression. The Grand Serology assay is therefore important because it may assigned specificity to peripheral immune responses that could highlight differential immunogenicity and eventual correlation with clinical variables.

TCRseq with Immunoseq's Platform from Adaptive Biotechnology:

Sequencing of the CDR3 variable region of the beta chain of the T cell receptor has been used for many years as a metric of T cell repertoire diversity and clonality. Although this method is not able to predict the specificity of T cells solely based on TCR nucleotide/amino-acid usage, it is a sufficient surrogate to detect specific clonal expansions or contractions, entropy, and tracking of clones, based on extensive available literature. Because of Adaptive Biotech's dominance and pioneering work in this field, we propose to outsource samples from PBMCs to them, using recommended SOPs. Therefore, internal validation efforts within CIMAC are so far minimal, since the assay will be performed in a centralized manner by an external vendor.

Nevertheless, the assay is expected to yield information about changes in T cell repertoire from baseline to post-treatment, as well as to differences observed based on combinations in each study arm. Importantly, this assay will gain more functional insight if it is also performed in parallel at the tumor tissue site, to establish clones that appear there and that are also in circulation, in order to track their evolution over treatment arms in the periphery.

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