Supplemental Appendix Table of Contents

Supplemental Methods

Statistical Analysis of PFS and OS

Analysis of PFS and OS followed protocol specified definitions and journal policies. The primary endpoint was PFS, defined as the date of randomization to the first observation of progressive disease or death due to any cause as reported by sites. Patients last known to be alive and without report of progression were censored at last date of contact. Key secondary endpoints included the incidence of adverse events, OS – defined as the time from date of randomization to death due to any cause.

The primary analysis of PFS used a stratified log rank test statistic and is reported as two-sided test. Stratified Cox regression was used to estimate treatment hazard ratios for treatment effect. For both the primary endpoint (PFS) and secondary endpoint (OS), 95% two-sided intervals are reported. The Kaplan-Meier method was used to estimate PFS and OS curves. Assessment of proportional hazards was based on Grambsch and Therneau (1994)[1] in the context of the cure rate model assumed for treatment effect.

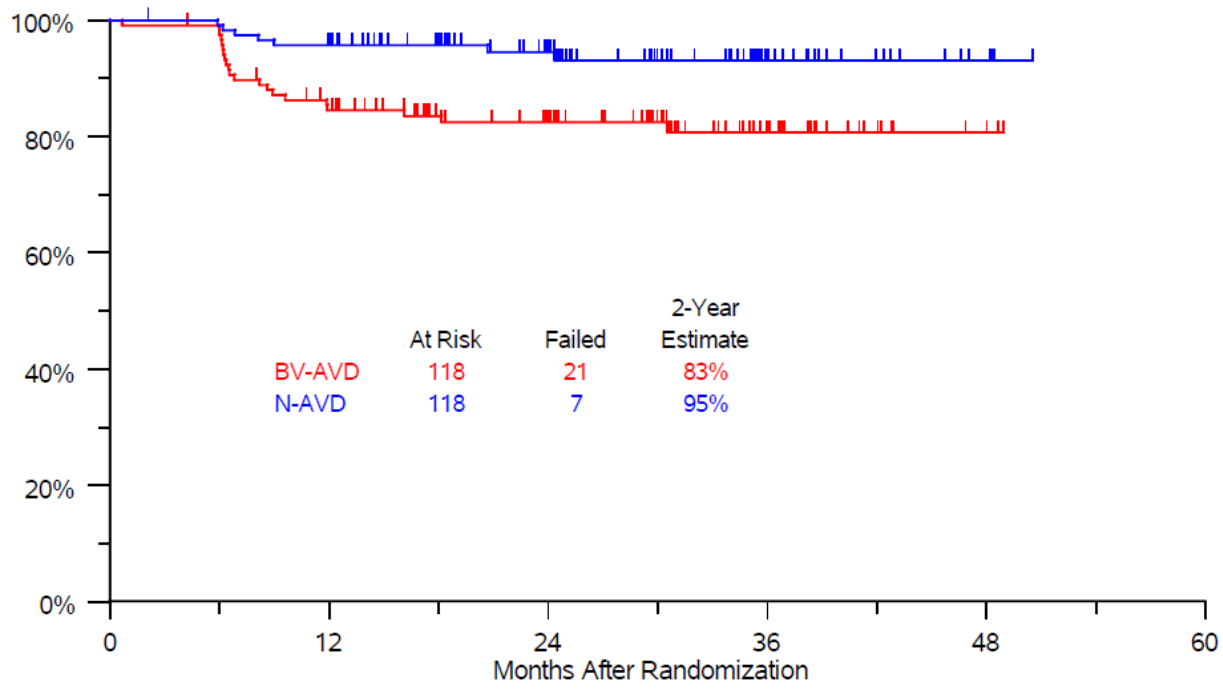
Forest plots for PFS did not include a provision for correction for multiplicity. Corresponding hazard ratios are presented with 95% confidence intervals on the basis of univariate Cox regression without adjustment for multiplicity; thus, the intervals should not be used in place of a subgroup hypothesis test.

Because the study protocol did not include a provision for correcting for multiplicity when conducting tests for secondary endpoints or in subgroups, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of a hypothesis test.

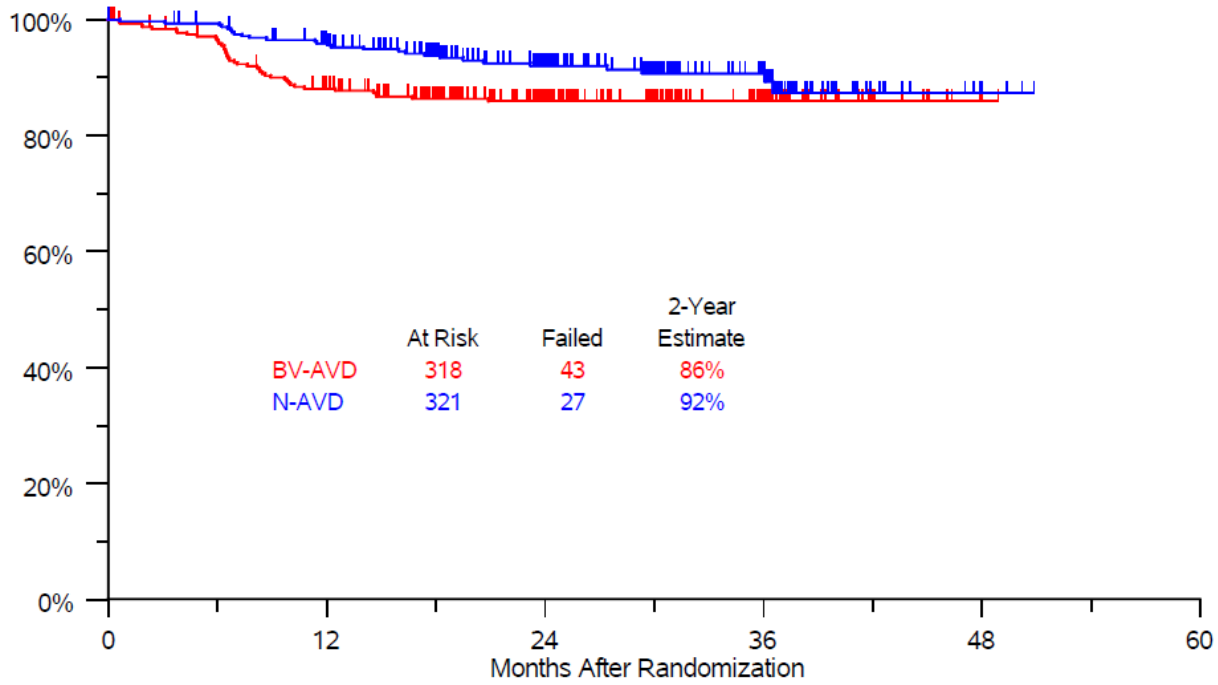
Figure S1: Progression-Free Survival by Age Subgroup in Modified Intent-to-treat Analysis Set (70% information fraction).

Panel (A) displays PFS in patients ages 12-17 years old, Panel (B) displays PFS in patients ages 18-60 years old, and Panel (C) displayes PFS in patients older than 60 years old.

(A)



(B)


100%
80%
60%
40%
20%
0%
0
12
24
36
48
60
Months After Randomization
At Risk
Failed
2-Year Estimate
BV-AVD 318 43 86%
N-AVD 321 27 92%

(C)

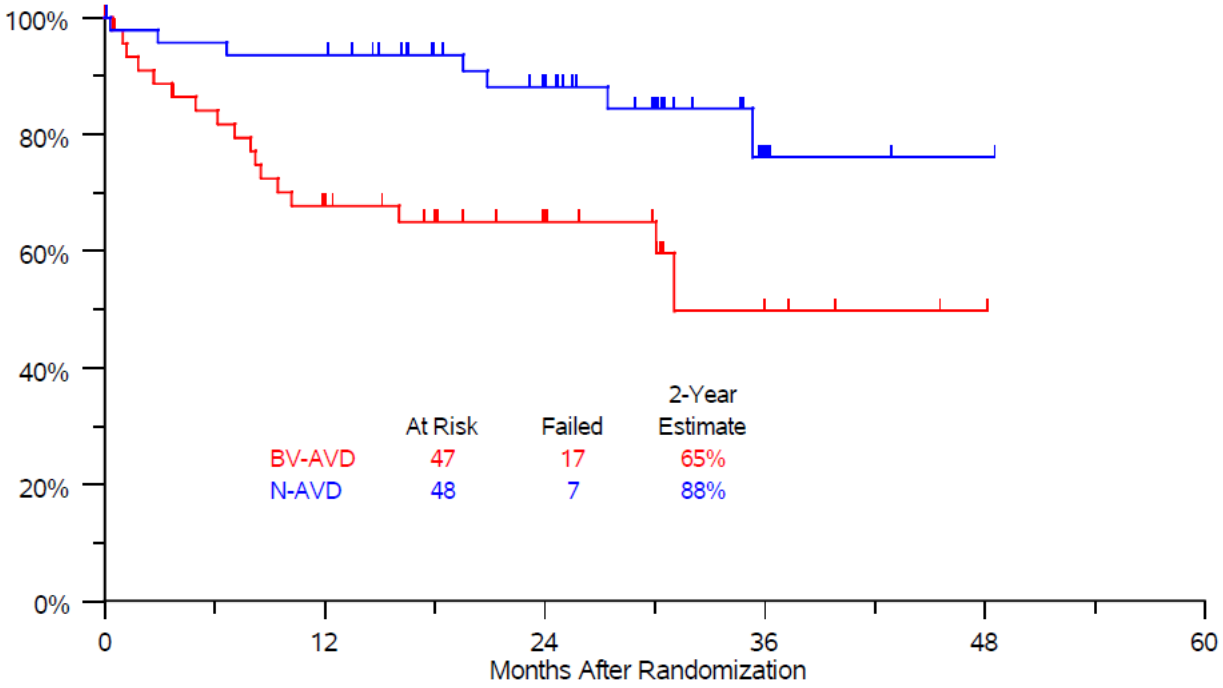

100%
80%
60%
40%
20%
0%
0
12
24
36
48
60
Months After Randomization
At Risk
Failed
2-Year Estimate
BV-AVD 47 17 65%
N-AVD 48 7 88%

Figure S2: Event-Free Survival (stratified) in Modified Intent-to-treat Analysis Set

EFS displayed by arm with a median follow-up of 2.1 years.

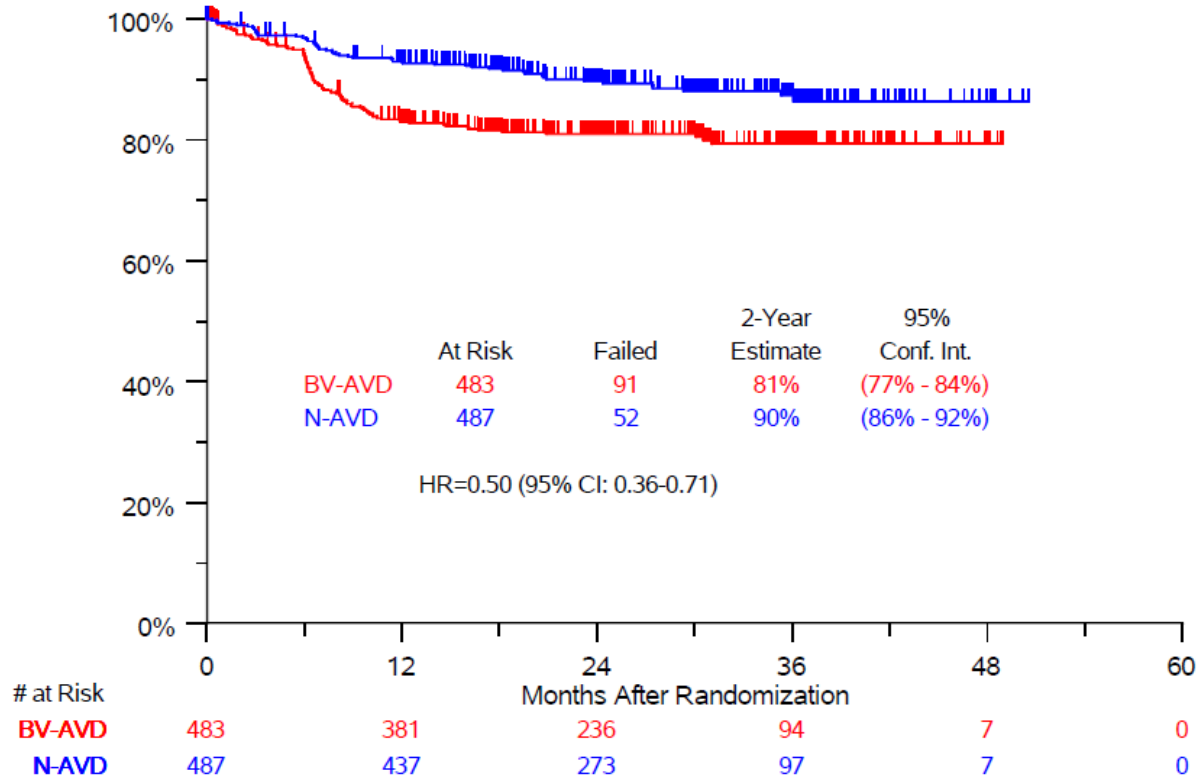


Table S1: Disposition of Patients by Arm in in Modified Intent-to-treat Analysis Set

	Total		Nivolumab + AVD		Brentuximab Vedotin + AVD	
	n	%	*n*	%	*n*	%
Eligible Patients	970	100.0%	487	100.0%	483	100.0%
Completed treatment	875	90.2%	450	92.4%	425	88.0%
Discontinued all treatment early	95	9.8%	37	7.6%	58	12.0%
Adverse event	40	4.1%	20	4.1%	20	4.1%
Refusal unrelated to AE	22	2.3%	9	1.8%	13	2.7%
Progression/relapse	9	0.9%	0	0	9	1.9%
Death	11	1.1%	3	0.6%	8	1.7%
Other – not protocol specified	13	1.3%	5	1.0%	8	1.7%
Any discontinuation of Bv or Nivolumab*	153	15.8%	46	9.4%	107	22.2%
Discontinued Bv or Nivo, but continued other agents**	78	8.0%	19	3.9%	59	12.2%
Received any G-CSF	741	76.4%	274	56.3%	467	96.7%
Dexrazoxane Use	273	28.1%	142	29.2%	131	27.1%
Major protocol deviation	11	1.1%	5	1.0%	6	1.2%
Lost to follow-up	4	0.4%	3	0.6%	1	0.2%
Consent withdrawal after treatment initiation	35	3.6%	15	3.1%	20	4.1%

*Excluded 5 patients who did not start protocol treatment in N-AVD arm, 6 patients who did not start protocol treatment in BV-AVD arm

**Included patients who did not complete the protocol treatment and discontinued all other agents after Bv or Nivo discontinued

Table S2: Per Protocol End-of-Treatment Radiation in Modified Intent-to-treat Analysis Set

	N-AVD (n=487)		BV-AVD (n=483)		Total (n=970)	
	N	%	N	%	N	%
Planned use of protocol-specified radiotherapy	286	59%	287	59%	573	59%
Received protocol-specified radiotherapy	3	0.6%	4	0.8%	7	0.7%

Table S3: End-of-treatment Metabolic Response by Arm in Modified Intent-to-treat Analysis Set

	Total		*Nivolumab + AVD*		*Brentuximab Vedotin + AVD*	
	n	*%*	*n*	*%*	*n*	*%*
Eligible Patients who had PET-CT scan performed at EOT	894	100.0%	456	100.0%	438	100.0%
Deauville Score						
1	217	24.3%	125	27.4%	92	21.0%
2	295	33.0%	166	36.4%	129	29.5%
3	167	18.7%	88	19.3%	79	18.0%
4	85	9.5%	39	8.6%	46	10.5%
5	73	8.2%	16	3.5%	57	13.0%
X	49	5.5%	18	3.9%	31	7.1%
Not Reported	8	0.9%	4	0.9%	4	0.9%
Deauville Score Group						
1-3	679	76.0%	379	83.1%	300	68.5%
4-5	158	17.7%	55	12.1%	103	23.5%
X	49	5.5%	18	3.9%	31	7.1%
Not Reported	8	0.9%	4	0.9%	4	0.9%

Table S4: Types of Event-Free Survival Event by Arm in Modified Intent-to-treat Analysis Set

Type of EFS Event	N-AVD N=487	BV-AVD N=483
Non-protocol chemotherapy prior to progression	10 (2.1%)	7 (1.4%)
Non-protocol radiation prior to progression	3 (0.6%)	5 (1.0%)
Progression/Relapse	32 (6.6%)	67 (13.9%)
Death without progression	7 (1.4%)	12 (2.5%)
Total EFS events	52 (10.7%)	91 (18.8%)

EFS = event-free survival; N-AVD = nivolumab, doxorubicin, vinblastine, dacarbazine; BV-AVD = brentuximab vedotin, doxorubicin, vinblastine, dacarbazine

Table S5: Causes of Death by Arm in Modified Intent-to-treat Analysis Set

Cause of Death	N-AVD N=487	BV-AVD N=483
Infection/Sepsis	4	6
Lymphoma	1	2
Medical issues other than cancer	2	4
New primary malignancy	0	1
Unknown	0	1
Total	7	14

N-AVD = nivolumab, doxorubicin, vinblastine, dacarbazine; BV-AVD = brentuximab vedotin, doxorubicin, vinblastine, dacarbazine

Table S6: Number of Deaths by Arm and Age Strata in Modified Intent-to-treat Analysis Set

	AGE: 12 - 17				*AGE: 18 - 60*				*AGE: > 60*			
	Nivolumab + AVD		*Brentuximab Vedotin + AVD*		*Nivolumab + AVD*		*Brentuximab Vedotin + AVD*		*Nivolumab + AVD*		*Brentuximab Vedotin + AVD*	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Eligible Patients	118	100.0%	118	100.0%	321	100.0%	318	100.0%	48	100.0%	47	100.0%
Vital Status												
Death	0	0	1	0.8%	4	1.2%	4	1.3%	3	6.3%	9	19.1%
Alive	118	100.0%	117	99.2%	317	98.8%	314	98.7%	45	93.8%	38	80.9%

Table S7: Complete Listing of All Adverse Events at least Possibly Related to Study Treatment by Arm in Modified Intent-to-treat Analysis Set. Adverse events with no entries for grades 2 to 5 are not included.

	Nivolumab + AVD (n=482) Grade					Brentuximab Vedotin + AVD (n=476) Grade				
ADVERSE EVENTS	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Abdominal pain	36	18	4	0	0	64	33	10	0	0
Acute kidney injury	0	0	2	0	0	0	0	2	1	0
Adrenal insufficiency	0	1	1	0	0	0	0	0	0	0
Agitation	3	1	0	0	0	0	0	0	0	0
Alkaline phosphatase increased	50	3	1	0	0	79	2	0	0	0
Allergic reaction	0	2	2	0	0	1	5	0	0	0
Alopecia	63	40	0	0	0	50	74	0	0	0
ALT increased	112	26	18	4	0	144	34	23	0	0
Amenorrhea	0	1	0	0	0	0	5	0	0	0
Amnesia	0	2	0	0	0	0	0	0	0	0
Anal fissure	0	0	0	0	0	0	1	0	0	0
Anemia	105	56	29	0	0	104	70	41	2	0
Anorectal infection	0	0	1	0	0	0	0	0	0	0
Anorexia	34	25	2	0	0	48	51	7	0	0
Anxiety	8	11	0	0	0	15	14	0	0	0
Appendicitis	0	0	1	0	0	0	0	0	0	0
Arthralgia	46	16	2	0	0	43	9	6	0	0
Arthritis	1	3	0	0	0	0	0	0	0	0
AST increased	102	11	9	3	0	130	16	13	1	0
Atelectasis	1	0	0	0	0	0	1	0	0	0
Atrial fibrillation	0	1	0	0	0	0	0	1	0	0
Autoimmune disorder	0	0	1	0	0	0	0	0	1	0
Back pain	16	11	0	0	0	23	6	4	0	0
Bacteremia	0	0	0	0	0	0	2	0	0	0
Bladder infection	0	1	0	0	0	0	1	0	0	0
Bloating	6	1	0	0	0	11	7	0	0	0
Blood bilirubin increased	7	1	3	0	0	5	6	3	0	0
Blood/lymph disorder-Other	2	1	0	0	0	4	1	0	0	0
Blurred vision	10	1	0	0	0	13	2	0	0	0
Bone pain	23	14	3	0	0	56	31	9	0	0
Brachial plexopathy	0	0	0	0	0	0	1	0	0	0
Bronchial infection	0	2	0	0	0	0	0	0	0	0
Bronchospasm	0	1	0	0	0	0	0	0	0	0
Bruising	2	0	0	0	0	7	1	0	0	0
Bullous dermatitis	0	0	0	0	0	0	1	0	0	0

	Nivolumab + AVD (n=482) Grade					Brentuximab Vedotin + AVD (n=476) Grade				
ADVERSE EVENTS	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Buttock pain	0	1	0	0	0	0	0	0	0	0
Cardiac arrest	0	0	0	0	0	0	0	0	2	0
Cardiac disorder-Other, spec	2	2	1	0	0	0	0	0	0	0
Cardiac troponin T increased	0	0	1	0	0	0	0	0	0	0
Catheter related infection	0	0	1	0	0	0	1	2	0	0
Chest pain - cardiac	2	2	0	0	0	0	0	0	0	0
Chest wall pain	1	0	1	0	0	1	0	0	0	0
Chills	20	1	0	0	0	19	1	0	0	0
Chronic kidney disease	0	1	0	0	0	0	0	0	0	0
Colitis	1	4	1	0	0	1	1	4	0	0
Colonic obstruction	0	0	0	0	0	0	0	1	0	0
Confusion	2	0	2	0	0	2	0	0	0	0
Conjunctivitis	0	1	0	0	0	3	1	1	0	0
Conjunctivitis infective	0	0	0	0	0	0	1	1	0	0
Constipation	164	28	1	0	0	146	50	8	0	0
Cough	26	7	0	0	0	23	8	0	0	0
CPK increased	1	0	0	0	0	0	1	0	0	0
Creatinine increased	25	2	0	0	0	10	3	0	0	0
Cyanosis	0	1	0	0	0	0	0	0	0	0
Dehydration	4	6	4	0	0	4	18	9	0	1
Delirium	0	0	0	0	0	0	0	1	0	0
Depression	6	3	0	0	0	7	2	0	0	0
Diarrhea	68	24	8	0	0	93	27	9	0	0
DIC	0	1	0	0	0	0	0	0	0	0
Dizziness	28	1	0	0	0	36	4	0	0	0
DLOC	1	0	0	0	0	1	0	0	1	0
Dry mouth	17	2	0	0	0	29	3	0	0	0
Dry skin	14	1	0	0	0	15	0	0	0	0
Dysgeusia	24	11	0	0	0	44	15	0	0	0
Dyspepsia	13	20	0	0	0	11	10	0	0	0
Dysphagia	3	4	1	0	0	3	4	0	0	0
Dyspnea	31	7	3	1	0	39	14	3	2	0
ECG QT corrected int prolong	0	0	1	0	0	0	0	0	0	0
Eczema	2	0	0	0	0	2	3	1	0	0
Edema face	0	1	0	0	0	4	1	0	0	0
Edema limbs	14	1	1	0	0	15	1	0	0	0
Ejection fraction decreased	0	2	1	0	0	0	2	1	0	0
Endocrine disorders-Other	6	3	0	0	0	0	0	0	0	0
Enterocolitis	0	1	1	0	0	0	1	0	0	0
Enterocolitis infectious	0	0	1	0	0	0	2	2	0	0

	Nivolumab + AVD (n=482)					Brentuximab Vedotin + AVD (n=476)				
	Grade					Grade				
ADVERSE EVENTS	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Erectile dysfunction	1	1	0	0	0	0	0	0	0	0
Erythroderma	0	0	1	0	0	0	0	0	0	0
Esophageal pain	0	0	1	0	0	0	0	0	0	0
Esophagitis	1	0	1	0	0	1	2	0	0	0
Extrapyramidal disorder	0	1	0	0	0	1	1	0	0	0
Facial muscle weakness	0	1	0	0	0	0	0	0	0	0
Fall	4	0	1	0	0	8	1	0	0	0
Fatigue	156	67	5	0	0	151	81	10	0	0
Febrile neutropenia	0	0	27	1	0	0	0	27	6	0
Fever	39	18	5	0	0	42	17	2	0	0
Fibrinogen decreased	0	2	0	0	0	0	0	0	0	0
Flatulence	4	0	0	0	0	4	2	0	0	0
Flu like symptoms	3	1	0	0	0	3	0	0	0	0
Flushing	8	2	0	0	0	2	0	1	0	0
Folliculitis	2	0	0	0	0	0	1	0	0	0
Fracture	0	0	0	0	0	0	1	0	0	0
Gait disturbance	0	0	0	0	0	1	1	0	0	0
Gastric hemorrhage	0	0	0	0	0	0	0	1	0	0
Gastritis	2	4	3	0	0	3	5	0	0	0
Gastroparesis	0	0	0	0	0	0	1	0	0	0
Gen disorders/admin site cond	6	0	0	0	0	1	4	0	0	0
Generalized edema	0	1	0	0	0	0	0	0	0	0
Generalized muscle weakness	11	5	0	0	0	16	7	2	0	0
GERD	12	14	0	0	0	14	25	0	0	0
GGT increased	2	0	2	0	0	3	1	0	0	0
GI disorders-Other, specify	8	3	0	0	0	8	4	0	2	0
Guillain-Barre syndrome	0	0	0	0	0	0	0	0	1	0
Hand-Foot syndrome	1	0	0	0	0	1	1	0	0	0
Headache	44	24	1	0	0	67	6	2	0	0
Heart failure	0	0	2	0	0	0	0	1	0	0
Hematuria	3	0	1	0	0	0	0	0	0	0
Hemolysis	0	0	1	0	0	0	0	0	0	0
Hemorrhoids	4	0	0	0	0	0	1	0	0	0
Hepatic failure	0	0	2	0	0	0	0	0	0	0
Hepatobil disorders-Other	0	1	1	0	0	0	0	1	0	0
Herpes simplex reactivation	0	1	0	0	0	2	1	0	0	0
Hiccups	3	2	1	0	0	11	0	0	0	0
Hoarseness	0	0	0	0	0	3	1	0	0	0
Hot flashes	6	3	0	0	0	19	0	0	0	0
Hypercalcemia	3	2	0	1	0	8	1	1	0	0

	Nivolumab + AVD (n=482) Grade					Brentuximab Vedotin + AVD (n=476) Grade				
ADVERSE EVENTS	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Hyperglycemia	51	3	3	0	0	57	3	3	0	0
Hyperhidrosis	8	6	0	0	0	10	5	0	0	0
Hyperkalemia	3	1	1	0	0	4	0	0	0	0
Hypermagnesemia	3	0	1	0	0	3	0	0	0	0
Hypertension	15	23	3	0	0	13	22	8	0	0
Hyperthyroidism	11	2	0	0	0	0	0	0	0	0
Hypertriglyceridemia	2	0	0	0	0	0	2	0	0	0
Hyperuricemia	4	0	1	0	0	6	0	0	0	0
Hypoalbuminemia	22	18	2	0	0	27	10	2	0	0
Hypocalcemia	23	10	0	0	0	23	10	1	0	0
Hypoglycemia	5	2	0	0	0	4	1	1	0	0
Hypokalemia	25	1	3	0	0	41	7	14	0	0
Hypomagnesemia	3	1	0	0	0	17	4	0	0	0
Hyponatremia	23	5	1	0	0	43	9	2	0	0
Hypophosphatemia	10	1	0	0	0	13	5	1	0	0
Hypotension	7	6	4	0	0	7	6	5	0	0
Hypothyroidism	13	21	1	0	0	2	1	0	0	0
Hypoxia	0	2	1	0	0	0	1	2	0	0
Ileus	0	0	0	0	0	0	3	1	0	0
Infections/infestations-Other	6	6	5	1	0	5	3	4	0	0
Infusion related reaction	6	25	5	0	0	3	7	0	0	0
Infusion site extravasation	0	2	0	0	0	0	2	0	0	0
INR increased	1	0	2	0	0	1	0	0	0	0
Insomnia	20	8	1	0	0	26	26	2	0	0
Investigations-Other, specify	11	1	1	0	0	8	2	0	0	0
Irregular menstruation	3	1	0	0	0	5	0	0	0	0
Laryngopharyngeal dysesthesia	0	1	0	0	0	0	0	0	0	0
Lethargy	3	0	0	0	0	1	1	0	0	0
Leukocytosis	0	0	2	0	0	0	0	6	0	0
Libido decreased	3	3	0	0	0	3	0	0	0	0
Lip infection	1	2	0	0	0	0	0	0	0	0
Lipase increased	1	0	1	0	0	0	1	0	0	0
Lung infection	0	4	5	1	0	0	6	8	0	0
Lymph gland infection	0	0	1	0	0	0	0	0	0	0
Lymph node pain	1	0	0	0	0	2	1	0	0	0
Lymphocyte count decreased	39	34	26	4	0	28	40	27	14	0
Lymphocyte count increased	0	3	1	0	0	0	10	0	0	0
Malaise	6	2	0	0	0	2	1	0	0	0
Memory impairment	7	1	0	0	0	4	0	0	0	0
Meningitis	0	0	1	0	0	0	0	0	0	0

	Nivolumab + AVD (n=482) Grade					Brentuximab Vedotin + AVD (n=476) Grade				
ADVERSE EVENTS	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Metab/nutrition disorders-Oth	5	0	0	0	0	0	1	1	0	0
Movements involuntary	0	1	0	0	0	2	0	0	0	0
MS/connective tissue disorder	3	1	1	0	0	4	1	0	0	0
Mucosal infection	0	1	0	0	0	0	1	0	0	0
Mucositis oral	64	34	9	0	0	55	34	11	0	0
Muscle cramp	13	1	0	0	0	15	3	1	0	0
Muscle weakness lower limb	2	3	0	0	0	3	3	1	0	0
Muscle weakness trunk	0	0	1	0	0	0	0	0	0	0
Muscle weakness upper limb	0	1	0	0	0	1	1	0	0	0
Myalgia	40	11	1	0	0	41	15	1	0	0
Myositis	1	0	1	0	0	0	0	0	0	0
Nail infection	1	2	0	0	0	2	0	0	0	0
Nasal congestion	6	0	0	0	0	10	3	0	0	0
Nausea	196	109	7	0	0	198	117	16	0	0
Neck edema	3	0	0	0	0	0	2	0	0	0
Neck pain	4	0	0	0	0	2	1	0	0	0
Nervous sys disorders-Other	2	2	0	0	0	5	2	0	0	0
Neutrophil count decreased	14	26	99	133	0	15	19	49	77	0
Non-cardiac chest pain	10	6	0	0	0	13	3	0	0	0
Oral dysesthesia	4	1	0	0	0	6	0	0	0	0
Oral pain	26	3	1	0	0	23	1	0	0	0
Pain	27	12	4	0	0	21	10	1	0	0
Pain in extremity	17	4	1	0	0	26	8	2	0	0
Palpitations	5	2	0	0	0	2	0	0	0	0
Pancreatitis	0	1	3	0	0	0	0	1	0	0
Papulopustular rash	4	0	0	0	0	2	1	0	0	0
Paresthesia	32	3	1	0	0	36	6	1	0	0
Paronychia	0	1	0	0	0	1	1	0	0	0
Paroxysmal atrial tachycardia	1	1	0	0	0	0	0	0	0	0
Pelvic pain	1	0	0	0	0	0	1	1	0	0
Pericardial effusion	0	1	0	0	0	0	0	0	0	0
Pericarditis	0	3	0	0	0	0	0	0	0	0
Peripheral motor neuropathy	13	7	1	0	0	12	17	6	0	0
Peripheral sensory neuropathy	98	36	5	0	0	115	112	39	0	0
Pharyngitis	0	0	0	0	0	0	1	0	0	0
Phlebitis	0	3	0	0	0	0	4	0	0	0
Photophobia	1	0	0	0	0	1	1	0	0	0
Photosensitivity	1	0	0	0	0	1	1	0	0	0
Platelet count decreased	36	7	4	5	0	63	7	8	8	0
Pleural effusion	0	1	1	0	0	0	0	0	1	0

	Nivolumab + AVD (n=482)					Brentuximab Vedotin + AVD (n=476)				
	Grade					Grade				
ADVERSE EVENTS	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Pneumonitis	1	7	3	0	0	1	4	7	2	1
Presyncope	0	2	0	0	0	0	3	0	0	0
Productive cough	2	0	0	0	0	1	1	0	0	0
Proteinuria	0	1	0	0	0	2	0	0	0	0
Pruritus	39	7	0	0	0	20	5	0	0	0
Psych disorders-Other, spec	1	0	0	0	0	2	1	0	0	0
Pulmonary edema	0	0	1	0	0	0	0	0	1	0
Rash acneiform	16	1	0	0	0	11	1	0	0	0
Rash maculo-papular	43	7	4	0	0	44	14	0	0	0
Rash pustular	0	0	0	0	0	0	1	0	0	0
Rectal fissure	0	0	0	0	0	0	1	0	0	0
Rectal pain	1	0	0	0	0	2	1	1	0	0
Renal/urinary disorders-Other	0	1	0	0	0	1	0	0	0	0
Resp/thoracic/mediastinal ds	2	1	0	0	0	3	2	0	0	0
Respiratory failure	0	0	0	0	0	0	0	0	3	0
Restrictive cardiomyopathy	0	1	0	0	0	0	0	0	0	0
Rhabdomyolysis	0	1	0	0	0	0	0	0	0	0
Salivary duct inflammation	0	1	0	0	0	0	2	0	0	0
Seizure	1	0	1	0	0	0	1	0	0	0
Sepsis	0	0	3	2	3	0	0	8	4	4
Sinus bradycardia	1	0	0	0	0	2	0	0	1	0
Sinus tachycardia	8	9	0	0	0	18	3	3	0	0
Skin hyperpigmentation	8	0	0	0	0	6	2	0	0	0
Skin hypopigmentation	2	1	0	0	0	0	0	0	0	0
Skin infection	2	4	0	0	0	1	6	3	0	0
Skin/subq tissue ds-Other	12	4	0	0	0	13	5	0	0	0
Small intestinal obstruction	0	0	0	0	0	0	0	1	0	0
Somnolence	0	0	0	0	0	0	1	0	0	0
Sore throat	12	3	1	0	0	26	1	0	0	0
Spasticity	0	1	0	0	0	1	0	0	0	0
Stomach pain	8	2	0	0	0	7	3	0	0	0
Stroke	0	0	1	0	0	0	0	0	0	0
Superficial thrombophlebitis	0	3	0	0	0	0	3	0	0	0
Supraventricular tachycardia	0	0	0	0	0	0	1	0	0	0
Syncope	0	0	1	0	0	0	0	2	0	0
Tendon reflex decreased	0	1	0	0	0	1	0	0	0	0
Thromboembolic event	1	6	4	1	0	0	4	5	0	0
Thrush	2	5	0	0	0	4	10	0	0	0
Tooth infection	0	1	0	0	0	0	0	0	0	0
Toothache	3	0	0	0	0	1	1	0	0	0

	Nivolumab + AVD (n=482) Grade					Brentuximab Vedotin + AVD (n=476) Grade				
ADVERSE EVENTS	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Tracheal mucositis	0	0	0	0	0	0	0	1	0	0
Tracheitis	0	1	0	0	0	0	0	0	0	0
Tremor	3	1	0	0	0	3	0	0	0	0
Tumor lysis syndrome	0	0	1	0	0	0	0	1	0	0
Typhlitis	0	0	0	0	0	0	0	3	0	0
Upper GI hemorrhage	0	0	1	0	0	0	0	0	0	0
Upper respiratory infection	0	5	1	0	0	0	7	1	0	0
Urinary tract infection	0	5	2	0	0	0	10	2	0	0
Urticaria	0	1	0	0	0	2	0	0	0	0
Vaginal infection	0	2	0	0	0	2	2	0	0	0
Vasc disorders-Other, spec	1	0	2	0	0	0	1	0	0	0
Vascular access complication	0	1	0	0	0	0	0	2	0	0
Vasovagal reaction	0	0	0	0	0	0	0	1	0	0
Ventricular arrhythmia	0	1	0	0	0	0	0	1	0	0
Ventricular tachycardia	0	1	0	0	0	0	0	0	1	0
Vertigo	1	1	0	0	0	1	0	0	0	0
Vision decreased	0	2	1	0	0	0	0	0	0	0
Vomiting	76	49	9	0	0	84	60	12	0	1
Watering eyes	1	0	0	0	0	4	1	0	0	0
Weight gain	3	7	3	0	0	4	4	0	0	0
Weight loss	17	8	0	0	0	30	30	11	0	0
White blood cell decreased	48	76	61	12	0	33	34	35	26	0
Wound infection	0	0	0	0	0	0	1	0	0	0
MAX. GRADE ALL HEM TOXICITIES	49	50	114	137	0	66	57	71	86	0
MAX. GRADE ALL NON-HEM TOXICITIES	91	228	119	10	3	54	204	168	17	6
MAX. GRADE ANY ADVERSE EVENT	44	112	159	142	3	47	153	153	94	6

Table S8: Grade ≥ 3 Adverse Events by Arm (≥ 3% of patients) by Arm in Modified Intent-to-treat Analysis Set

Adverse Event Type	N-AVD n = 482 Grade ≥ 3 No (%)	BV-AVD n = 476 Grade ≥ 3 No (%)
Neutrophil count decreased	232 (48%)	126 (26%)
White blood cell decreased	73 (15%)	61 (13%)
Anemia	29 (6%)	43 (9%)
Lymphocyte count decreased	30 (6%)	41 (9%)
Febrile neutropenia	28 (6%)	33 (7%)
ALT increased	22 (5%)	23 (5%)
Peripheral sensory neuropathy	5 (1%)	39 (8%)
AST increased	12 (2%)	14 (3%)
Platelet count decreased	9 (2%)	16 (3%)
Sepsis	8 (2%)	16 (3%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; N-AVD = nivolumab, doxorubicin, vinblastine, dacarbazine; BV-AVD = brentuximab vedotin, doxorubicin, vinblastine, dacarbazine

Table S9: Possible Immune-Related Adverse Events by Arm in Modified Intent-to-Treat Analysis Set. Note: List includes AEs (e.g. ALT increased) that were not confirmed to be immune-related but are included here for completeness.

	Nivolumab + AVD (n=482) Grade					Brentuximab Vedotin + AVD (n=476) Grade				
ADVERSE EVENTS	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	0	1	1	0	0	0	0	0	0	0
ALT increased	112	26	18	4	0	144	34	23	0	0
Arthralgia	46	16	2	0	0	43	9	6	0	0
Arthritis	1	3	0	0	0	0	0	0	0	0
AST increased	102	11	9	3	0	130	16	13	1	0
Blood bilirubin increased	7	1	3	0	0	5	6	3	0	0
Diarrhea	68	24	8	0	0	93	27	9	0	0
Enterocolitis	0	1	1	0	0	0	1	0	0	0
Esophagitis	1	0	1	0	0	1	2	0	0	0
Guillain-Barre syndrome	0	0	0	0	0	0	0	0	1	0
Hyperthyroidism	11	2	0	0	0	0	0	0	0	0
Hypothyroidism	13	21	1	0	0	2	1	0	0	0
Lipase increased	1	0	1	0	0	0	1	0	0	0
Myositis	1	0	1	0	0	0	0	0	0	0
Pancreatitis	0	1	3	0	0	0	0	1	0	0
Pneumonitis	1	7	3	0	0	1	4	7	2	1
Rash acneiform	16	1	0	0	0	11	1	0	0	0
Rash maculo-papular	43	7	4	0	0	44	14	0	0	0
Seizure	1	0	1	0	0	0	1	0	0	0
Serum amylase increased	1	0	0	0	0	0	0	0	0	0

Table S10: Representativeness of Trial Population

Supplementary Table on the Representativeness of Study Participants on S1826	
Disease, problem, or condition under investigation	Classic Hodgkin lymphoma (inclusive of all cHL histologies)
Special considerations related to sex	Hodgkin lymphoma affects more males than females. Expected rates by sex: 2.9 per 100,000 males and 2.3 per 100,000 females per year.[1] In economically disadvantaged areas outside of North America boys < 15 years of age have a five-fold higher incidence of HL than girls.
Age	The hallmark of Hodgkin lymphoma epidemiology is its variation in occurrence by age at diagnosis. The median age of diagnosis is 39 years old. However, in the United States and North America a bimodal incidence is noted, with the first peak occurring from ages ~15-30 and a later peak occurring from ages ~65-80. Patients under the age of 20 years old account for 12.3% of new cHL cases, patients ages 20-34 account for 31% of cHL new diagnoses, and 20.2% of new cHL diagnoses are accounted for by patients ages 65 years and above.
Race or ethnic group	The incidence of cHL in all races among men is 2.8 new cases per 100,000 persons and 2.3 new cases per 100,000 among women. The incidence rate of cHL is highest among non-Hispanic white persons, with incidence rates of 3 new cases per 100,000 persons. The incidence of cHL among Hispanic persons is 2 new cases per 100,000 persons. The incidence of cHL among non-Hispanic black patients is 2 new cases per 100,000 persons.[1]
Geography	The distribution of cHL and its histologic subtypes differs between economically developed settings compared to settings with depressed socioeconomic factors, and by the age of exposure to Epstein-Barr virus and the prevalence of HIV.
Overall representativeness of this trial (S1826)	The proportion of males and females enrolled on the present trial match the population incidence rates of classical Hodgkin lymphoma, with a predominance among male patients (trial participants 56% male and 44% female). The participants in the present trial also demonstrated the expected proportions of White, Black, American Indian, Asian, and Hispanic populations based on Hodgkin lymphoma incidence rates in the United States. In the current trial, 76% of enrolled patients identified as Non-Hispanic White, 12% were Black, 13% were Hispanic, and 3% were Asian. Among the 9% patients listed as “other“ in **Table 1**, patients identified as Pacific Islander (n=2), Native American (n=3), multiracial (n=9), and unknown (n=81, 8%). Participants enrolled in this trial represent 256 National Cancer Institute National Clinical Trials Network institutions, including NCI Community Oncology Research Program sites, that are geographically diverse across the United States and Canada and serve patients from a wide range of demographics. Overall, S1826 was a demographically representative trial, representative of the North American cHL population.

cHL = classic Hodgkin lymphoma; HIV = human immunodeficiency virus

References

1. Grambsch PM, Therneau TM. Proportional Hazards Tests and Diagnostics Based on Weighted Residuals. Biometrika 1994;81:515-26.