TITLE: Phase II Study of Durvalumab (MEDI4736) (anti-PD-L1) and Trametinib (MEKi) in MSS Metastatic Colon Cancer.

Coordinating Center: *University of Texas MD Anderson Cancer Center*

Principal Investigator: Michael Overman, MD
Department of Cancer Medicine
1515 Holcombe Blvd, Unit 1360
Houston, TX 77030
Telephone: (713) 792-2828
Fax: 713-745-1163
moverman@mdanderson.org

Agent(s)/Supplier: Medimmune(AstraZeneca)/Novartis

Version: 2 dated December 19, 2017

TABLE OF CONTENTS

Page

2017-0514
December 19, 2017
Page 1

ABBREVIATIONS

ACS	American Cancer Society
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CEA	carcinoembryonic antigen (CEA)
CFR	Code of Federal Regulations
CRC	colorectal cancer
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
ECG	electrocardiogram
FDA	United States Food and Drug Administration
ICH	International Committee on Harmonisation
IP	Investigational Product
IRB	Institutional Review Board
MG	Milligram
MTD	maximum tolerated dose
PD	progressive disease
PFS	progression-free survival
OTC	over-the-counter
OS	overall survival
RBC	red blood cells
RECIST	Response Evaluation Criteria In Solid Tumors
RR	response rate
SAE	serious adverse event
HNSCC	head and neck squamous cell carcinoma
UG	Microgram
WBC	white blood cell

1. OBJECTIVES

1.1. **Primary Objective/Endpoint**

1.1.1. **Objective**

1.1.1.1. To determine efficacy of this combination as assessed by the immune-related response rate

1.1.2. **Endpoint**

1.1.2.1. Best overall response rate (CR+PR) by immune-related response rate.

1.2. **Secondary Objectives/Endpoints**

1.2.1. **Objectives**

1.2.1.1. To assess the safety and tolerability of the combination in this population.
1.2.1.2. Additional efficacy assessments of treatment activity
1.2.1.3. To evaluate the immune microenvironment and systemic changes as a result of treatment.

1.2.2. **Endpoints**

1.2.2.1. To assess the safety and tolerability of the combination in this population.
1.2.2.2. Progression free survival as determined by irRC
1.2.2.3. Time to treatment failure by irRC
1.2.2.4. Disease control rate and duration of stable disease
1.2.2.5. Overall survival
1.2.2.6. Change in immune cell composition as determined by comparative analysis of pre- and post-treatment tumor biopsies, and peripheral blood samples.
1.2.2.7. Exploratory analysis of efficacy endpoints according to CMS subtype

2. BACKGROUND

2.1 ***Study Disease***

2.1.1 **Colon Cancer Background and Treatment Options**

Colorectal cancer (CRC) is the third most common cancer in the United States with an estimated 136,830 new cases and 50,310 deaths in 2014 [1]. Approximately 20-25% of CRC patients will have distant metastatic disease at the time of diagnosis, and an additional 40-50% of patients will eventually develop CRC liver metastases (CRCLM) [2]. While treatment of early stage disease is highly successful with 5-year survival rates over 70%, this rate drops to approximately 10% in the metastatic setting. Front-line treatment options for metastatic

disease typically involve 5-FU based regimens along with oxaliplatin, irinotecan, bevacizumab, cetuximab, and durvalumab. Patient can achieve excellent disease control in the first and second line settings with various combination regimens. Unfortunately, patients will typically progress after their tumors become resistant to these therapies. There are currently two approved agents in the 3rd line setting, regorafenib and TAS-102, but these are typically either poorly tolerated or are of limited benefit.

2.1.2 **Colorectal cancer and Immune function**

Significant progress has been made in the characterization of colorectal tumor micro-environment, and there is evidence that CRC is an immune sensitive malignancy. Regulatory T cells accumulate in CRC and as a consequence suppress cytotoxic and helper T-cell activity [Svensson 2012]. More importantly, there is strong evidence that the presence of immune cells in CRC is predictive of patient outcomes. Intratumoral density of T cells including cytotoxic (CD8+) and memory (CD45RO+) has been shown to negatively correlate with risk of recurrence in early stage CRC [Pages 2009]. In any stage of disease, decreased density of CD8+ lymphocytic infiltrate is associated with primary tumor growth and metastatic progression [Mlecnik 2011, Pages 2005]. Efforts by Galon and colleagues have shown than an immune score based on T-cell infiltration significantly predicts disease-free and overall survival. Further, T-cell infiltration of liver metastases is common, and positively correlates with survival [Katz 2013]. Improved survival is significantly associated with number of CD4+ and a higher proportion of CD8+ T-cells, while worse outcomes are seen with greater proportions of Treg cells. There is a strong association between the presence of a cytotoxic infiltrate and disease control at any stage and at metastatic sites of disease.

2.1.3 **Immune Checkpoint Inhibition in CRC**

Checkpoint blockade has already been found to be successful in treating mismatch repair deficient CRC. The initial results from the first study of PD-1 blockade with the antibody pembrolizumab report excellent disease control in this population [Le 2015]. 78% of patients demonstrated immune-related progression free survival and 40% had an immune-related objective response. Within the same study, all patients with microsatellite stable disease progressed on therapy. This suggests that there are important difference between the MSI and MSS populations, and that checkpoint blockade monotherapy is likely to be insufficient to generate a response in the majority of MSS patients.

2.2 **Investigational Agents**

2.2.1 **Durvalumab Background**

Durvalumab is a human immunoglobulin G (IgG)1 kappa mAb directed against human PD-L1. Durvalumab is expressed in Chinese hamster ovary cells and has an overall molecular weight of approximately 149 kDa. Durvalumab selectively binds with high affinity to human PD-L1 and blocks its ability to bind to the PD-1 and CD80 receptors, respectively. The fragment crystallizable (Fc) domain of durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fc gamma receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity (ADCC) [38].

2.2.2 **Durvalumab Pre-Clinical Experience**

Programmed cell death 1 (CD279) is a member of the immunoglobulin superfamily of molecules involved in regulation of T-cell activation. It is found on T cells, B cells, macrophages, NK cells, dendritic cells, and mast cells. It has also been described on peripheral tissues including cardiac endothelium, lung, small intestine, keratinocytes, islet cells of the pancreas, and syncytiotrophoblasts in the placenta as well as a variety of tumor cell types [39-45]. **Programmed** cell death ligand 1 (CD274, B7-H1) is constitutively expressed on many hematopoietic cells, but may be upregulated in hematopoietic and non-hematopoietic cells. Regulation of PD-L1 is mediated, in part, by type I and type II interferon (IFN). Programmed cell death ligand 2 (PD-L2; B7-DC) was identified in 2001 [43, 46]. Its expression is far more restricted and is confined to hematopoietic cells. Engagement of PD-1 on T cells inhibits activation with downstream effects on cytokine production, proliferation, cell survival, and transcription factors associated with effector T-cell function [47-52].

Durvalumab has shown the following activity as an anti-PD-L1 molecule:

- Durvalumab binds to PD-L1 and blocks its interaction with PD-1 and CD80.
- Durvalumab can relieve PD-L1-mediated suppression of human T-cell activation in vitro.
- Durvalumab inhibits tumor growth in a xenograft model via a T-cell-dependent mechanism.
- A surrogate anti-mouse PD-L1 antibody resulted in improved survival in a syngeneic tumor model as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy.
- In the same study, anti-mouse PD-L1 antibody-treated mice were completely tumor free 3 months after tumor implantation and demonstrated long-term immunity during re-challenge.
- In a subsequent study in the same syngeneic model, the combination of an anti-mouse PD-L1 antibody and anti-CTLA-4 antibody resulted in complete tumor regression in all mice treated.

- Prevalence of PD-L1 expression on the surface of human tumors, ranging from approximately 0% to 35%, was demonstrated in a broad survey of samples derived from tumor types of interest.

The cynomolgus monkey is considered to be the only relevant nonclinical species for evaluation of local and systemic toxicities of Durvalumab. In addition, in vivo in cynomolgus monkeys, Durvalumab suppresses soluble programmed cell death ligand 1 (sPD-L1) in serum and fully occupies membrane PD-L1 on various leukocyte subsets at doses equal to or more than 0.1 mg/kg (lowest dose tested) with a dose-related duration of suppression and occupancy.

In general, there were no Durvalumab-related adverse effects in toxicology studies conducted in cynomolgus monkeys with Durvalumab that were of relevance to humans. Adverse findings in the non-Good Laboratory Practice (GLP) pharmacokinetic (PK)/pharmacodynamic and dose range-finding study (4 doses over 5 weeks), and a GLP 4-week repeat-dose toxicity study were consistent with antidrug antibody (ADA)-associated morbidity and mortality in individual animals. The spectrum of findings, especially the clinical signs and microscopic pathology, in a single animal in the GLP, 4-week, repeat-dose study was also consistent with ADA immune complex deposition, and ADA:Durvalumab immune complexes were identified in a subsequent non-GLP, investigative immunohistochemistry (IHC) study. Similar observations have been reported by MedImmune in cynomolgus monkeys administered human mAbs unrelated to Durvalumab. Given that immunogenicity of human mAbs in nonclinical species is not generally predictive of responses in humans, the ADA-associated morbidity and mortality were not taken into consideration for the determination of the no-observed-adverse-effect level (NOAEL) of Durvalumab. Interim audited data from the dosing phase of the pivotal 3-month GLP toxicity study with Durvalumab in cynomolgus monkeys showed that subchronic dosing of Durvalumab was not associated with any adverse effects. Therefore, the NOAEL of Durvalumab in all the general toxicity studies was considered to be 100 mg/kg, the highest dose tested in these studies. In addition to the in vivo toxicology data, no unexpected membrane binding of Durvalumab to human or cynomolgus monkey tissues was observed in GLP tissue cross-reactivity studies using normal human and cynomolgus monkey tissues. Finally, in vitro cytokine release studies showed that Durvalumab did not induce cytokine release in blood from any donor.

2.2.3 **Durvalumab Clinical Experience**

As of July 12, 2016, across the entire clinical development program, an estimated 4067 patients have been exposed to 1 or more doses of durvalumab in ongoing AstraZeneca

sponsored Phase I to III studies, either as monotherapy or in combination and 5911 patients where the treatment arm is blinded. Additionally, approximately 4000 patients have been exposed to 1 or more doses of durvalumab in ESR/IITs. Estimates of overall cumulative patient exposure based on actual exposure data from any completed clinical trials and the enrolment/randomisation schemes for ongoing open label and blinded trials are: 3723 patients received durvalumab monotherapy and 3372 patients received durvalumab in combination with tremelimumab. No AstraZeneca or MedImmune studies have been completed and no study has terminated prematurely due to toxicity. The total post-marketing exposure to durvalumab from May 2017 to the 12 July 2017 was estimated to be approximately 1.46 patient-years.

Study CD-ON-MEDI4736-1108: NSCLC: As of 24 October 2016, 304 NSCLC patients had received durvalumab monotherapy of whom 272 comprised the full analysis set (FAS, defined as all patients who had measurable disease at baseline per blinded independent central review [BICR] and who had an opportunity to be followed for at least 24 weeks by the DCO date of the 24 October 2016. The objective response rate (ORR), was 22.6% and 4.6% in PD-L1 positive (defined as having tumour cells [TX] ≥25%) and negative patients, respectively. The 12-month OS rate was 55.8% and 38.8% in PD-L1 positive and negative patients, respectively. HNSCC: As of 29 April 2016, 62 patients with recurrent/metastatic SCCHN had received durvalumab monotherapy. Among seven responders, six patients had a DOR for ≥12 months with longest DOR being 19.8 months. Six and 12 month OS is 62% and 42%, respectively. Urothelial Carcinoma: As of DCO on 24 October 2016, 191 patients had been enrolled into the urothelial cell cohort. The ORR was numerically higher in the PD-L1 high (TC ≥25% or IC ≥25%) subgroup (27.6%) compared with the PD-L1 low/negative (TC <25% and IC <25%) subgroup (5.1%); and 17.8% overall regardless of PDL1 expression. The median TTR was 1.41 months (range 1.2 to 7.2); the median DOR has not yet been reached (range 0.9+ to 19.9+). At the DCO, 26 of 34 responders (76.5%) had an ongoing response; 17 patients had a DOR ≥ 6 months and 10 patients had a DOR ≥9 months. The disease control rate (DCR, defined as any complete response (CR)/partial response (PR) or stable disease (SD) >6 weeks) by BICR assessment was 36.6% (95% CI: 29.8, 43.9). The median PFS by BICR assessment was 1.5 months (95% CI: 1.4, 1.9). The PFS rate at 6 months was 21.7% (95% CI: 15.8, 28.3). The median OS was 18.2 months (95% CI: 8.1, not estimable); the OS rate at 6, 9 and 12 months was 64.0% (95% CI: 56.2, 70.9), 57.5% (95% CI: 47.2, 66.5), and 55.0% (95% CI: 43.9, 64.7), respectively. Results for all efficacy endpoints were similar between the UC cohort (As-treated Population) and the 2L+ post-platinum UC subgroup (As-treated Population). HCC: Of the 970 patients in the total 10 mg/kg group, 40 had HCC and were included in the HCC cohort, which was analyzed for efficacy using a DCO of the 24 October

2016. ORR, based on RECIST v1.1 was 10% (95% CI: 2.8, 23.7). The median PFS was 2.7 months (95% CI: 1.4, 5.3). The PFS rate at 12 months was 20.7% (95% CI: 9.2, 35.3). The median OS was 13.2 months (95% CI: 6.3, 21.1); the OS rate at 6, 9 and 12 months was 76.5% (95% CI: 59.6, 87.0), 62.3% (95% CI: 44.7, 75.8) and 56.1% (95% CI: 38.4, 70.5), respectively. Other indications: In PD-L1 unselected patients, the ORR, based on investigator assessment per RECIST v1.1, ranged from 0% in uveal melanoma to 17.4% in advanced cutaneous melanoma, and DCR-24w ranged from 4.2% in TNBC to 39.1% in advanced cutaneous melanoma. Across the PD-L1 high tumours, ORR was >10% for advanced cutaneous melanoma (33.3%). In the PD-L1 positive subset, DCR-24w was >10% in advanced cutaneous melanoma (66.7%).

Study D4190C00007: As of the DCO of 03 May 2016 among the 40 patients with MDS treated in Study D4190C00007, the best overall responses were mCR in 13 patients (32.5%); SD in 6 patients (15.0%); and PD in 12 patients (30.0%). The remaining 9 patients (22.5%) did not meet the criteria for complete remission, mCR, partial remission, SD, or PD at the date of assessment.

ATLANTIC: A total of 444 patients were enrolled and treated in ATLANTIC (111 in Cohort 1 [EGFR/ALK+], 265 in Cohort 2 [ERK/ALK wild type] and 68 in Cohort 3 [ERK/ALK wild type] [TC ≥90%]). Of these 444 patients, 28 (6.3%) patients were still on treatment at the time of the 03 June 2016 DCO, and 78 (17.6%) patients had completed 12 months of treatment. Durvalumab demonstrated good clinical activity based on ORR in patients with locally advanced or metastatic NSCLC who had received at least 2 prior systemic treatment regimens across various subgroups. In the PD-L1 unselected patients (ie, pre-enrichment) in the EGFR/ALK wild type/unknown Cohort 2, the ORR was 10.4% (95% CI: 6.2, 16.2). The response rate in Cohort 2 was numerically higher in the PD-L1 high (TC ≥25%) patients compared with PD-L1 low/negative patients (16.4%, 95% CI: 10.8, 23.5; versus 7.5%, 95% CI: 3.1, 14.9). In all cohorts, the response rate was similar between the non-squamous patients and the full population with the same PD-L1 expression cut off. The response rate was numerically higher with the higher PD-L1 cut off (TC ≥90%): 30.9% (95% CI: 20.2, 43.3) in Cohort 3 (TC ≥90%) and 23.2% (95% CI: 16.4, 31.1) in the combined Cohorts 2 and 3 with PD-L1 TC ≥90%. Responses were observed in the EGFR/ALK+ Cohort 1, but the rate was generally lower than the other cohorts (12.2%, 95% CI: 5.7, 21.8 for the PD-L1 high [TC ≥25%] group; 3.6%, 95% CI: 0.1, 18.3 for the PD-L1 low/negative group). Good durability was seen across responders. For patients who responded, the response was durable across various subgroups (median DOR in Cohort 2, which had 12 months of follow up: not reached for the PD-L1 unselected group; 12.3 months in the PD-L1 high [TC ≥25%] group; and not

reached for the PD-L1 low/negative group). However, the data were limited by the length of follow-up for Cohort 1 (EGFR/ALK+) and Cohort 3 (TC ≥90%), which had at least 6 months of follow-up. The median OS was highest in the PD-L1 high (TC ≥25%) patients with the OS rate at 6 and 12 months of 67.4% and 47.7%, respectively, in Cohort 2. For the PD-L1 unselected patients, the OS rate at 6 and 12 months was 58.4% and 37.9%, respectively. For the PD-L1 low/negative patients, the OS rate at 6 and 12 months was 60.3% and 34.5%, respectively.

PACIFIC: As of the DCO, 13 February 2017, 476 and 237 patients with NSCLC were randomized to the durvalumab and placebo arms respectively. The median PFS by BICR was significantly longer with durvalumab treatment (16.8 months [95% CI: 13.0, 18.1]) compared with placebo (5.6 months [95% CI: 4.6, 7.8]); stratified hazard ratio for disease progression or death, 0.52; 95% CI: 0.42, 0.65; p<0.001. The 12 month PFS rate was 55.9% (95% CI: 51.0, 60.4) with durvalumab vs 35.3% (95% CI: 29.0, 41.7) with placebo and the 18 month PFS rate was 44.2% (95% CI: 37.7, 50.5) with durvalumab vs 27.0% (95% CI: 19.9, 34.5) with placebo. PFS improvement with durvalumab was demonstrated across all pre-specified subgroups and irrespective of pre-cCRT PD-L1 expression (hazard ratios, 0.59; 95% CI: 0.43, 0.82 for TC <25%, and 0.41; 95% CI: 0.26, 0.65 for TC ≥25%).

ORR was 28.4% (126/443 patients; 95% CI: 24.3, 32.9) in the durvalumab group compared with 16.0% (34/213 patients; 95% CI: 11.3, 21.6) in the placebo group. OS data were considered immature at the time of analysis.

The median DOR was longer in the durvalumab group; 72.8% vs 46.8% of patients had ongoing response at 18 months compared with placebo. The median time to death or distant metastasis was longer with durvalumab than with placebo (23.2 months vs 14.6 months; P<0.001).

HAWK: As of the DCO, 31 March 2017, 111 patients with HNSCC were treated with durvalumab, had measurable disease at baseline and were evaluable. Durvalumab demonstrated clinically meaningful antitumour activity in patients with PD-L1 high (≥25% TC) HNSCC. ORR, based on BICR assessment using RECIST v1.1 was 16.2% (95% CI: 9.90, 24.41). The median duration of treatment was 3.45 months (range 0.3 to 12.2 months) and the median time to onset of response was 2.0 months (range 1.64 to 9.20 months). Responses appeared durable with 55% of patients having ongoing responses at the DCO. The median PFS was 2.1 months (95% CI: 1.9, 3.7). The median OS was 7.1 months (95% CI: 4.9, 9.9); the OS rate at 12 months was 33.6% (95% CI: 24.8, 42.7).

Study CD-ON-MEDI4736-1161: Of the 68 patients with metastatic or unresectable melanoma treated with the combination of durvalumab and BRAFi/MEKi, 65 patients were evaluable for response (DCO 21 August 2015). A total of 37 patients (54.4%) had a best overall response of confirmed or unconfirmed CR and PR. The confirmed DCR (CR + PR + SD) for ≥12 weeks was 73.5%.

All 67 patients who have been treated in Study CD-ON-MEDI4736-1161 had at least 1 AE (Table 34). Overall, the most frequently reported (>10% patients) AEs (all grades, regardless of causality) in order of decreasing frequency were diarrhea (58.2%); fatigue (47.8%); pyrexia (41.8%); vomiting (37.3%); chills and nausea (32.8% each); decreased appetite (31.3%); arthralgia and rash (28.4% each); pruritus (26.9%); asthenia and edema peripheral (25.4% each); constipation, cough and headache (23.9% each); dry mouth (22.4%); dyspnoea (20.9%); anemia, blood creatine phosphokinase increased and dermatitis acneiform (19.4% each); abdominal pain and rash maculo-papular (17.9% each); AST increased, folliculitis and myalgia (16.4% each); ALT increased, hyperhidrosis and insomnia (14.9% each); dizziness and pain in extremity (13.4%); back pain, influenza-like symptoms and night sweats (11.9%); and alopecia and hypertension (10.4%).

Thirty-four of 67 treated patients (50.7%) reported SAEs. SAEs occurring in >1 patient by order of decreasing frequency were: pyrexia (6 patients); vomiting (4 patients); atrial fibrillation, diarrhea, ejection fraction decreased and nausea (3 patients each); anemia, asthenia, gastrointestinal hemorrhage, thrombosis and transaminases increased (2 patients each).

Ten patients (14.9%) permanently discontinued treatment with investigational products due to AEs. These events included choroidal effusion, GGT increased, infusion-related reaction, ILD, liver function test increased, platelet count decreased, oedema, paraesthesia, tubulointerstitial nephritis and transaminases increased (1 patient each). Three deaths have been reported in this study. One death from Cohort A resulted from an event of metastases to meninges, 1 death from Cohort B resulted from an event of cardiopulmonary failure and the other death from Cohort C resulted from an event of pyrexia. None of the events were considered related to investigational product. A total of 61 patients (91.0%) treated with study drugs experienced at least 1 AESI (Table 35). The most common AESI was (grouped term) diarrhea (39 patients [58.2%]). Other common AESIs (grouped term) were: rash (35 patients [52.2%]); dermatitis (28 patients [41.8%]); select hepatic events (16 patients [23.9%]); and select renal events (9 patients [13.4%]). There was an increased incidence of

events in the diarrhea, rash, dermatitis and select renal events categories compared to the durvalumab monotherapy pool.

The PK profiles of durvalumab as monotherapy and in combination with tremelimumab are described based on data from key studies. Based on population PK modelling, the estimated half-life of durvalumab is approximately 17 days following 10 mg/kg Q2W dose. Durvalumab monotherapy (Study CD-ON-MEDI4736-1108): As of 24 October 2016, PK data were available for 993 patients who have been treated with durvalumab 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W (dose escalation), 10 mg/kg Q2W (dose-expansion), and 20 mg/kg Q4W (dose-exploration) durvalumab administered as an iv infusion over 60 minutes. Following the first iv dose, durvalumab exhibited nonlinear PK at doses <3 mg/kg Q2W likely due to saturable target-mediated CL and exhibited linear PK at doses ≥3 mg/kg Q2W. The AUC0-14 increased dose-proportionally at doses of 3 to 20 mg/kg and more than dose proportionally at doses of <3 mg/kg, likely due to saturable target-mediated CL. Cmax increased in a dose-proportional manner within the dose range examined. The steady state was achieved at approximately Week 16. Accumulation of durvalumab was observed following repeated dosing. Mean AR ranged from 0.64 to 1.87 and 3.16 to 4.93 for Cmax and Ctrough, respectively.

The ADA profiles of durvalumab as monotherapy and in combination with tremelimumab are described based on data from key studies. Durvalumab monotherapy (Study CD-ON-MEDI4736-1108): As of 24 October 2016, a total of 835 patients provided samples for ADA analysis. Only 26 of 835 patients (3.1%) were ADA positive. Three patients were nAb positive. Based on population PK covariate analysis, ADA positive status was not associated with a clinically relevant reduction of exposure to durvalumab. At the 10 mg/kg Q2W dose, sPD-L1 suppression in ADA positive patients was similar to that observed in ADA negative patients. The relevance of ADA on safety and efficacy is unknown given the small number of ADA positive patients. Details on the safety and efficacy profile of durvalumab monotherapy and in combination with BRAF/MEKi are listed above. Refer to the current durvalumab Investigator's Brochure (v11) for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

2.2.4 **Trametinib background**

Trametinib (GSK/NOVARTIS1120212) is a selective MEK1 and MEK2 inhibitor with selective activity towards BRAF and RAS mutant cancer cell lines and hematopoietic cancer cells from AML and CML origins. Trametinib inhibited the proliferation of most of the BRAF mutant

melanoma cell lines tested (22 of 25), and it effectively inhibited the growth of BRAF mutant melanoma xenografts in vivo alone or in combination with dabrafenib. It causes inhibition of ERK phosphorylation leading to G1 cell cycle arrest and tumor xenograft growth inhibition in vivo following oral dosing.

2.2.4.1 **Biochemical characterization**

The in vitro activity of trametinib was evaluated using recombinant kinase domains of various kinases to determine the potency and selectivity of the compound. Trametinib was shown to be a potent and selective allosteric inhibitor of MEK1 and MEK2 (MEK1/MEK2). In a 3 protein coupled-enzyme system using BRAFV600E or truncated c-RAF and inactive MEK1 or MEK2 and inactive ERK, trametinib strongly inhibited the phosphorylation of ERK (IC50s 3.5 to 11 nM). Further investigations demonstrated the ability of trametinib to block BRAF catalyzed MEK1/MEK2 activation by binding to the unphosphorylated MEK1/MEK2 (IC50 =0.7 and 0.9 nM, respectively) as well as its ability to inhibit the kinase activity of phosphorylated MEK1/MEK2 (IC50=13.2 and 10.7 nM, respectively). Additional studies showed that trametinib strongly bound to the unphosphorylated MEK1 and had a very slow off-rate. Phospho-mapping by liquid chromatography with mass spectrometry (LC-MS) identified that trametinib blocks phosphorylation of Ser218 and not Ser222 on MEK1 by BRAFV600E. Inhibition by trametinib was noncompetitive with ATP.

Trametinib was evaluated to see if it had any direct action on molecules up-stream of MEK1/MEK2 in the MAP kinase pathway. Trametinib did not inhibit BRAF or CRAF kinase activity, as it did not affect the phosphorylation of myelin basic protein (MBP) mediated by BRAF or CRAF at concentrations up to 10 µM.

Trametinib was inactive against 44 other kinases screened at GSK/NOVARTIS (IC50>10 □M) and against 131 additional kinases tested at Institutes for Pharmaceutical Discovery, Branford, CT at a single concentration (inhibition <50% at 10 µM). It did not affect specific ligand bindings to 23 receptors or 7 non-kinase enzymes, indicating a high degree of selectivity. This property is explained by the fact that trametinib is a non-ATP competitive, allosteric binding inhibitor, and hence does not share the promiscuity observed with ATP-competitive kinase inhibitors. Therefore, trametinib is highly specific for the MEK1 and MEK2 kinases (Section 1.5.21.5.2) and is unlikely to have any significant off-target pharmacological activity.

In summary, trametinib is a potent and selective inhibitor of MEK1 and MEK2 kinase activity.

2.2.5 **Trametinib Pre-Clinical Experience**

2.2.5.1 **Safety Pharmacology**

In an exploratory modified neurobehavioral screen, a single oral dose of 100 mg/kg trametinib was administered to male rats. Subsequent studies showed that this dose leads to morbidity and mortality. Inhibition of body weight gain, diarrhea, prone position, blepharoptosis, piloerection, reduced spontaneous locomotion and mydriasis, were observed between 2 and 24 hours post dose. Comparable findings have not been observed in repeat dose toxicity studies at significantly lower, tolerated doses in rats and dogs, therefore, at relevant tolerated doses, trametinib is not considered to have any significant effects on general behavior, physiologic function or acute neurotoxicity.

No significant respiratory effects were seen in rats following single doses up to 0.125 mg/kg trametinib as assessed by measurement of ventilatory function and airway resistance. A dose of 0.125 mg/kg produced a mild, transient decrease in body temperature (up to 0.8°C) at 1 hour post dose, which by itself does not appear to result in significant toxicity. However, this dose was not tolerated in repeat dose studies in rats due to significant dermal toxicity.

Trametinib inhibited hERG channel repolarization in HEK293 cells with an IC_{50} of 1.54 µM (950 ng/mL). To determine the potential effect of hERG inhibition, a rabbit left ventricular wedge assay was performed, which demonstrated that trametinib had no significant effect on QT interval at concentrations up to 30 µM (18450 ng/mL; limit of solubility). However, significant decreases in isometric contractile force occurred at concentrations of 10 µM (6150 ng/mL) and 30 µM. Trametinib also decreased the Tp-e interval at a concentration of 30 µM. These effects occurred at concentrations which far exceed clinical exposures (Cmax of 22 ng/mL) at the therapeutic dose of 2 mg/day.

In an exploratory assessment of potential effects of trametinib on cardiovascular function, a single intravenous infusion of trametinib in dogs at 1 mg/kg (a dose that when given orally produced acute, severe morbidity) over 10 minutes (Cmax of 2.5 µM or 1500 ng/mL) produced no changes in electrocardiogram (ECG) parameters, blood pressure or heart rate during the 30 minute measurement period. In the definitive oral cardiovascular safety pharmacology study in dogs, single oral doses up to 0.075 mg/kg in dogs (a dose that produced morbidity following repeat dosing) produced no changes in arterial blood pressure, heart rate, body temperature or ECG intervals, including QTc.

In summary, while trametinib demonstrated effects on cardiac electrophysiology in vitro, the concentrations at which these effects were observed far exceed the free fraction concentrations of tolerated exposures in repeat dose toxicity studies in rats and dogs and steady state exposures in subjects at the proposed clinical dose of 2 mg/day. To date, there have been few significant clinical QTc or ECG effects observed in subjects taking trametinib.

2.2.5.2 **Pharmacokinetics and Product Metabolism in Animals**

The nonclinical pharmacokinetics of trametinib were similar across the species (mouse, rat, dog and monkey). Low plasma clearance relative to liver blood flow and generally long half-lives likely contribute to the accumulation upon repeat dosing which is consistent with observations in humans. Upon achieving steady-state, by 7 days for mice and by 3 weeks for rats and dogs (based on sparse sampling study design), the exposure of trametinib generally increased dose proportionally, which is consistent with observations in humans (steady state appeared to be achieved by Day 15).

The volume of distribution of trametinib was generally greater than total body water for all species, consistent with the observed wide distribution to tissues in the rat. There was no selective association of drug-related material with melanin containing tissues. Plasma protein binding was high in nonclinical species and humans (>95%). In vitro blood cell association in humans was concentration dependent with a high blood to plasma ratio (ranged from 3 to 8) at the clinically relevant trametinib concentrations of 1 and 10 ng/mL. Nonclinical species, including rats and dogs, showed protracted elimination of DRM (Drug Related Material) consistent with a high volume of distribution, long half-life, and the PK data of trametinib in subjects with solid tumors.

Absorption and systemic availability in nonclinical species and humans was moderate to high (>40% to approximately 100%). After absorption, the fecal route of elimination was the major excretory pathway in humans, rats and dogs. In humans, trametinib is eliminated predominantly by hydrolytic deacetylation, either deacetylation alone (M5) or in combination with mono-oxygenation (M7). The enzymes involved are likely hydrolytic enzymes, such as esterases or amidases that are not generally associated with drug interaction risks.

For the nonclinical species, trametinib was the major circulating component (> 60% of DRM) in plasma at all sampling time points. In humans, trametinib partitions in red blood cells and the majority of the circulating radioactivity is present as trametinib in blood (78-95% of

DRM). Three minor metabolites M5, M6 and M7 were identified with the deacetylated metabolite (M5), which was shown to have similar in vitro pharmacological activity as parent, accounting for ≤11% of plasma (rat and dog) or blood DRM (human). In an earlier investigation of plasma metabolites in humans following repeat dosing, the metabolites do not appear to accumulate to the same degree as parent. Qualitatively, all of the major metabolites of trametinib observed in humans have been detected in the nonclinical species.

Based on in vitro studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP3A4. Although trametinib was found to be an in vitro inhibitor of CYP2C8, CYP2C9 and 2C19, inducer of CYP3A4 and inhibitor of the transporters (OATP1B1, OATP1B3, Pgp and BCRP), its low efficacious dose, and low clinical systemic concentration (22.2 ng/mL or 0.04 µM at 2 mg) relative to the in vitro inhibition/induction potency suggests an overall low potential for drug-drug interactions.

2.2.5.3 **Toxicology**

The nonclinical toxicology findings associated with trametinib administration to mice, rats and dogs are consistent with pharmacologically mediated changes as a result of MEK1/MEK2 inhibition and disruption of MAPK signaling pathways. Trametinib caused adverse effects in a variety of tissues and systems (skin, gastrointestinal tract, phosphate homeostasis, liver, ovary, bone and hematological tissues) mainly at doses ≥0.03 mg/kg/day. The majority of the findings in mice and dogs appeared to be related to effects within the gastrointestinal tract, where in mice, effects were observed at or above clinical exposures and primarily consisted of perforation of the colon with secondary peritonitis and degeneration/necrosis of the glandular mucosa of the stomach, and in dogs presented clinically as decreased body weight, decreased food consumption and/or fecal abnormalities and occurred at subclinical exposures. In rats, tolerability was more dependent on changes occurring in skin over time and its effect on impaired barrier function. These findings may be related to those seen in the clinic in the form of skin rashes and diarrhea. Rats were more sensitive to trametinib with liver, phosphate homeostasis, soft tissue mineralization, bone, hematopoietic and ovary effects occurring at ≥0.016 mg/kg/day. Hepatic toxicity in rats given trametinib consisted of increased serum transaminases and, in mice and rats at higher doses, hepatocellular necrosis. Hyperphosphatemia and physeal thickening occurred in rats given trametinib and is likely caused by inhibition of MEK-dependent FGF signaling in kidney and bone, respectively. Hematological changes consisted of decreased bone marrow cellularity and, at higher doses, hematopoietic cell necrosis. While minor hematology changes have been observed

in the clinic, subjects taking trametinib have not demonstrated increased serum phosphorus.

In 13 week studies, systemic exposures (AUC) at the MTD in rats or NOAEL in dogs, which was also the MTD, were 0.3- and 0.4-times clinical steady state AUC, respectively. In the 26 week mouse study, the MTD was 0.1 mg/kg/day which was 1.0-times clinical steady state AUC.

Trametinib may impair female fertility in humans based on the reduction of corpora lutea in rats (0.3-times clinical steady state AUC). There were no effects on male reproductive organs in toxicology studies in rats or dogs, indicating that trametinib is unlikely to affect male fertility. In embryofetal development studies, maternal toxicity and developmental toxicity, including total loss of pregnancy and post-implantation loss, were observed in rats and/or rabbits given trametinib (0.3- and 0.1-times clinical steady state AUC, respectively). These effects are consistent with literature reports that inhibition of MEK1/MEK2 activity impacts granulosa cell survival and folliculogenesis, while genetic ablation of MEK1, ERK2 or skin-restricted MEK1/MEK2 has been shown to cause embryolethality and decreased progeny size. Taken together, trametinib treatment may result in adverse effects on pregnancy. There are no adequate and well-controlled studies of trametinib in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with trametinib. It is not known if trametinib is excreted in milk.

The principal effects of trametinib in juvenile rats were on growth (body weight and long bone length) and in bone, phosphate homeostasis, eye, skin, liver, heart and female reproductive system effects, consisting of a delay in a physical landmark of sexual maturity and mammary gland development, lower corpora lutea and lower ovarian weights. All of the female reproductive effects were reversible. With the exception of corneal mineralization/dystrophy and increased heart weight, similar effects have been observed in adult animals given trametinib.

The genotoxicity assessments conducted indicate that trametinib does not present a genotoxic hazard to humans. The requirement for male patients taking trametinib to use contraception with female partners of child bearing potential is not recommended based on absence of genotoxicity, no effects on male reproductive tissues in nonclinical toxicity studies, and the minimal potential for trametinib exposure of females via semen.

Although the concentration of trametinib in semen is unknown in humans and animals,

trametinib was non-genotoxic in preclinical in vivo and in vitro genotoxicity studies suggesting that the human risk to induce transmissible genetic damage via sperm from male subjects to female partners is low. The risk for exposure to a female partner of a man receiving trametinib therapy is also considered to be low based of the following assessment. At a daily dose of 2 mg, the estimated Cmax is 22 ng/mL. Assuming a similar disposition into semen, the estimated daily dose of trametinib to a pregnant partner via semen (assuming 2 ejaculations/day and 5 mL/ejaculation) would be 220 ng. The mean trametinib Cmax following an IV microtracer dose of 5 ug in humans was determined to be 0.105 ng/mL [Study MEK115064: Determination of the Absolute Bioavailability of Trametinib Following a Single Oral Dose Co-Administered with an Intravenous Radiolabelled Microdose of Trametinib in Subjects with Solid Tumors]. Assuming dose-exposure proportionality via intravenous administration, an intravenous dose of 220 ng would result in a Cmax of 0.00462 ng/mL. In pregnant rats, the no observed adverse effect level (NOAEL) for embryo fetal development effects was 0.016 mg/kg/day (mean AUC of 52.3 ng.h/mL and Cmax of 2.79 ng/mL), however in pregnant rabbits a NOAEL was not determined with the lowest observed adverse effect level (LOAEL) for maternal and embryo fetal development effects being 0.039 mg/kg/day (mean AUC of 31.9 ng.h/mL and Cmax of 2.10 ng/mL). Based on these data and assuming 100% absorption of trametinib from semen, the estimated exposure via semen would be approximately 1/450th the oral exposure (0.00462 ng/mL/ 2.10 ng/mL) achieved at the LOAEL dose for rabbit maternal and embryofetal toxicity and approximately 1/600th the oral exposure (0.00462 ng/mL/ 2.79 ng/mL) achieved at the NOAEL dose in pregnant rats. Taken together, this would suggest that the risk of embryofetal developmental toxicity as a consequence of exposure to female pregnant partners is very low.

In conclusion, the toxic potential of trametinib has been characterized in a comprehensive battery of preclinical studies. The effects observed in preclinical studies were generally, either directly or indirectly, associated with the pharmacologic inhibition of MEK1/MEK2 by trametinib and generally consistent with adverse effects observed in cancer patients. The data from these preclinical studies support the clinical use of trametinib under the proposed dose regimen.

2.2.6 **Trametinib Clinical Experience**

The effect of trametinib in subjects with a variety of refractory cancers is currently under evaluation in 9 clinical studies which are ongoing and 13 completed studies as of the IB cutoff date. Trametinib has been administered as monotherapy in 12 of these studies, and as combination therapy in the other 10 studies. Two additional ongoing studies are part of

a compassionate use program.

Trametinib pharmacokinetics were determined after single- and repeat-dose oral administration of trametinib tablets in subjects with solid tumors. Trametinib is absorbed rapidly with median Tmax generally occurring 1.50 hours after single oral administration of trametinib under fasting conditions. The absolute oral bioavailability of a single trametinib 2.0 mg tablet is moderate to high (72%) relative to a co-administered IV microdose. Single-dose administration of trametinib with a high-fat, high-calorie meal resulted in a 70% decrease in maximum observed concentration (Cmax), a 24% decrease in area under the concentration-time curve from time zero (pre-dose) to last time point (AUC(0-t)) and a 10% decrease in AUC extrapolated to infinity (AUC(0-τ)) compared to fasted conditions.

Following repeat-dosing the mean area under the curve (AUC0-τ) and maximum concentrations (Cmax) increased in an approximately dose proportional manner. Trametinib accumulates with repeat dosing with a mean accumulation ratio at the recommended dose of 2 mg once daily of 5.97 and a terminal half-life of 5.3 days determined after single dose administration. Steady state appears to be achieved by Day 15, with little difference in pre-dose (trough) concentration at the end of the dosing interval (Cτ), Cmax and area under the concentration-time curve from time zero (pre-dose) to 24 hrs (AUC(0-24)) between Days 15 and 21.

Trametinib is a low extraction ratio drug based on plasma IV clearance of 3.21 L/hr, which represents approximately 1% of liver blood flow. Trametinib has a high volume of distribution (Vd) of 1060 L determined following an IV microdose.

Fecal excretion is the major route of elimination after [^{14}C] trametinib oral dose, accounting for >80% of excreted radioactivity recovered (or 39.2 and 35.0% of the radioactive dose in 2 subjects) while urinary excretion accounted for <19% of excreted radioactivity recovered (<10% of the radioactive dose). Following a single dose of [^{14}C]-trametinib, approximately 50% of circulating radioactivity is represented as the parent compound. However, based on metabolite profiling after repeat dosing of trametinib, ≥75% of drug-related material in plasma is the parent compound.

In vitro and *in vivo* data suggest that trametinib is unlikely to affect the PK of other drugs and that the PK of trametinib is unlikely to be affected by other drugs. Trametinib is metabolized predominantly via deacetylation which is likely mediated by hydrolytic esterases which are not generally associated with drug interaction risk, nor is it a substrate

of P-gp or BCRP.

Based on the adverse events (AEs) observed in the dose escalation phase of the first-time-in-human (FTIH) study MEK111054, the maximum tolerated dose was established at 3.0 mg once daily, and the recommended Phase II dose (RP2D) of trametinib was identified as 2.0 mg once daily.

In the 12 monotherapy studies of trametinib for which data are available, all studies except one had AEs. In the studies with AEs, 50% to 100% of all subjects in any dose group had at least 1 AE, and 0% to 70% of all subjects in any dose group had at least 1 SAE. Of the studies with discontinuations or withdrawals, 3% to 26% of subjects receiving trametinib permanently discontinued study treatment or withdrew due to AEs.

Of the >700 subjects (including crossover subjects) in the 2.0 mg dose group, in 8 monotherapy studies with AEs, 50% to 100% of subjects had at least 1 AE, and 0% to 70% of all subjects had SAEs. Of the studies with discontinuations or withdrawals, 3% to 24% in the 2.0 mg does group permanently discontinued study treatment or withdrew from the study due to AEs.

In the 2.0 mg dose group across all 8 monotherapy studies with AEs, the most common AEs had were rash, diarrhea, fatigue, peripheral edema, nausea, acneiform dermatitis, vomiting, constipation, anemia, pruritus, alopecia, hypertension, decreased appetite, dyspnea and dry skin.

Of the >700 subjects in the 10 combination therapy studies of trametinib, 97% to 100% of subjects in any trametinib dose group had at least 1 AE, and 33% to 53% of subjects in any trametinib dose group had at least 1 SAE, and 5% to 26% permanently discontinued study treatment or withdrew due to AEs. In the combination trials for which data are available, the most common AEs had were fatigue, diarrhea, mucosal inflammation, thrombocytopenia, nausea, vomiting, rash, pyrexia, neutropenia, decreased appetite, acneiform dermatitis, anemia, peripheral edema, constipation, and stomatitis.

Table 1.3: Selected Adverse Reactions Occurring in >10% of Patients Receiving Trametinib. Patients with BRAF V600E or V600K mutation-positive metastatic melanoma received either 2 mg trametinib orally once daily or chemotherapy with either dacarbazine 1000 mg/m2 every 3 weeks or paclitaxel 175 mg/m2 every 3 weeks. In this study, 9% of patients receiving trametinib experienced adverse reactions resulting in permanent discontinuation of trial

medication. The most common adverse reactions resulting in permanent discontinuation of trametinib were decreased left ventricular ejection fraction (LVEF), pneumonitis, renal failure, diarrhea, and rash. Adverse reactions led to dose reductions in 27% of patients treated with trametinib. Rash and decreased LVEF were the most common reasons cited for dose reductions of trametinib.

	Trametinib (n=211)		Chemotherapy (n=99)	
	Any Grade, n(%)	Grade 3-4, n (%)	Any Grade, n(%)	Grade 3-4, n (%)
GASTROINTESTINAL DISORDERS				
Diarrhea	43	0	16	2
Stomatitis	15	2	2	0
Abdominal pain	13	1	5	1
INVESTIGATIONS				
Increased Aspartate aminotransferase	60	2	16	1
Increased Alanine aminotransferase	39	3	20	3
Hypoalbuminemia	42	2	23	1
Anemia	38	2	26	3
Increased Alkaline phosphatase	24	2	18	3
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Rash	57	8	10	0
Acneiform dermatitis	19	<1	1	0
Dry skin	11	0	0	0
Pruritis	10	2	1	0
Paronychia	10	0	1	0
VASCULAR DISORDERS				
Lymphedema	32	1	4	0
Hypertension	15	12	7	3
Hemorrhage	13	<1	0	0

2.3 **Rationale**

We hypothesize that the efficacy of immune-checkpoint inhibitors in microsatellite stable (MSS) CRC can be enhanced by better priming and T-cell activation of the intratumoral environment. We believe that combining systemic administration of MEK inhibition with an anti PD-L1 antibody will augment this T-cell activation in metastatic, MSS CRC.

Tregs accumulate in CRC and, as a consequence, suppress cytotoxic and helper T-cell activity. Improved survival is significantly associated with number of CD4+ and a higher proportion of CD8+ T-cells, while worse outcomes are seen with greater proportions of Treg cells. Importantly, while CRC has a relatively high degree of mutational heterogeneity [4], TCGA data suggests that fewer neo-epitopes are observed than expected [5]. These findings suggest

that immune stimulation in combination with checkpoint blockade inhibition may be more effective than checkpoint blockade monotherapy.

To activate the immune response in MSS disease, a different strategy is needed. Genetic differences between mismatch repair proficient and deficient patients correlate with differences in the tumor immune microenvironment that impact sensitivity to checkpoint blockade therapy. Llosa and colleagues [Llosa 2015] interrogated the immune microenvironment between a subset of CRC primary tumors that were either micro-satellite high or stable. They convincingly demonstrate that tumor immune microenvironment is distinct between these populations. Specifically, relative to MSS disease, MSI-high CRC is characterized by increased infiltration by T-cells with both cytotoxic and Th1 phenotypes, but also expression of high levels of inhibitory immune surface markers such as PD-1, PD-L1, CLTA-4.

MEK inhibition has been shown to alter the immune microenvironment in tumors. In pre-clinical models, Trametinib has been shown to have anti-tumor effects on the CT26 tumor model. This murine colorectal tumor cell line contains homozygous *KRAS* G12D mutation and MAPK1/MET amplifications [Castle 2014]. Liu et al showed that while Trametinib has modest suppression of tumors *in vivo*, this effect is enhanced by combination with PD-1 or PD-L1 blockade [Liu 2015]. Survival was also improved with combination therapy over either agent in monotherapy. Further, when timed with a 1-week lead in with Trametinib, a significant improvement in survival was observed.

A preliminary phase 1 study (n=20) utilizing a different PD1 and MEK inhibitor demonstrated efficacy of this combination with a 20% response rate in KRAS mutant CRC (all partial responses) [Bendall et al, 2016 ASCO Annual Meeting]. An additional 20% of patients experienced stable disease (lasting >6 months in 3 patients). No DLTs were observed. Further, these agents in combination had no therapy related grade 4 AEs and a 35% rate of grade 3 AEs, including diarrhea (9%), fatigue (4%), rash (4%), nausea (4%), maculopapular rash (4%), AST increase (4%), and vomiting. These were mostly attributable to the MEKi, with a 17% discontinuation rate for the MEKi. The most common AEs included diarrhea (70%), fatigue (52%), dermatitis acneiform (44%), rash (35%), nausea (26%), maculopapular rash (26%), pruritis (26%), AST increase (22%), creatinine increase (22%), peripheral edema (17%), stomatitis (17%), and vomiting (17%).

We believe that the combination of Durvalumab (a PD-L1 antibody) with Trametinib (MEK inhibitor) will be effective and safe in patients with metastatic MSS colorectal cancer.

Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data from a Phase I study (study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 subjects were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similar findings have been reported by others (32-35). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (34)]. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/ pharmacodynamics parameters (36).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed metastatic colorectal cancer.

3.1.2 Patients must have measurable disease per RECIST v1.1 criteria.

3.1.3 Patients must have had at least prior treatment with a fluoropyrimidine and either oxaliplatin or irinotecan.

3.1.4 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of this combination in patients <18 years of age, children are excluded from this study.

3.1.5 Body weight > 30kg.

3.1.6 Life expectancy of greater than 6 months.

3.1.7 ECOG performance status 0-1 (Karnofsky ≥70%; see Appendix 1).

3.1.8 Patients must have normal organ and marrow function as defined below:

- Leukocytes	≥3,000/mcL
- Absolute neutrophil count	≥1,500/mcL
- Hemoglobin	≥ 9.0g/dL
- Platelets	≥75,000/mcL
- Total bilirubin	< 1.5 X institutional normal limits (subjects with known Gilbert syndrome are eligible with total bilirubin < 3.0 mg/dL)
- AST(SGOT)/ALT(SGPT)	≤ 2.5 X institutional ULN (≤ 5 if liver metastases present)
- Creatinine	within normal institutional limits
OR	
- Creatinine clearance	> 40mL/min by Cockcroft-Gault or 24h urine collection.

3.1.9 Known MSS status by either IHC or PCR. Known or evaluable BRAF and KRAS status.

3.1.10 Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal subjects. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
-- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
-- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

3.1.11 Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately and will be removed from the study.

3.1.12 Ability to understand and the willingness to sign a written informed consent document.

3.1.13 Willingness to have 2 tumor biopsies; the first before and the second while on therapy (optional for all patients and may become mandatory in order to ensure 15 patients at MTD have paired biopsies).

3.2 **Exclusion Criteria**

3.2.1 Patients who have had chemotherapy within 2 weeks prior to first dose of study drug.

3.2.2 Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria:
-- Subjects with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Principal investigator.
-- Subjects with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Principal investigator.

3.2.3 Patients may not be receiving any other investigational agents.

3.2.4 Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of study medication. Note: Local sugery of isolated lesions for palliative intent is acceptable.

3.2.5 Patients with known brain metastases or leptomeningeal carcinomatosis will be excluded from this clinical trial. Patients with suspected brain metastases at screening should have an MRI (preferred) or CT each prefereably with IV contrast of the brain prior to study entry.

3.2.6 Mean QT interval corrected for heart rate (QTc) ≥ 470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction.

3.2.7 History of pneumonitis or interstitial lung disease (ILD).

3.2.8 History of allogenic organ transplantation.

3.2.9 Subjects with active, known, or suspected autoimmune disease including patients with a history of inflammatory bowel disease (ulcerative colitis or Crohn's disease); patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis (e.g., Wegener's granulomatosis), and central nervous system or motor neuropathy considered of autoimmune origin (e.g., Guillain-Barre Syndrome, myasthenia gravis, multiple sclerosis). Subjects with vitiligo, type I diabetes mellitus, Grave's disease, Hashimoto thyroiditis, psoriasis, and other mild autoimmune disease not requiring systemic treatment are permitted to enroll at the discretion of the investigator.

3.2.10 Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug

administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

3.2.11 Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Subjects, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.

3.2.12 Prior exposure to T cell checkpoint inhibitor therapies.

3.2.13 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirements, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

3.2.14 History of active primary immunodeficiency.

3.2.15 Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice for patients suspected of having active infection), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Subjects with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

3.2.16 Female subjects who are pregnant or breastfeeding or male or female subjects of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of study medications.

3.2.17 Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

4. REGISTRATION PROCEDURES

This is a single institution study. It will be publically registered on the national clinic trial database online at https://clinicaltrials.gov/

5. TREATMENT PLAN

5.1 Study Design

This study is an open-label, single center phase 2 trial assessing the efficacy and safety of combination intravenous durvalumab with oral trametinib. At trial initiation, the first patients will be enrolled at the target doses for the combination durvalumab and trametinib identified in earlier melanoma trials as safe and well tolerated; durvalumab at 1500mg q4w with trametinib 2mg PO daily. De-escalation doses will be available if this dose proves toxic in the colon population (figure 1). After study initiation, up to 6 patients will be enrolled and if the number of DLTs <2, this will be considered the MTD of the combination. If the number of DLTs>/=2, additional 6 patients will be treated at the lower dose level. The dose level with <2 DLTs out of 6 patients will be deemed as the MTD for the combination.

Dose Level	Durvalumab (IV)	Trametinib (PO)
-2	1500mg q4w	1mg daily
-1	1500mg q4w	1.5mg daily
1	1500mg q4w	2mg daily

Figure 1: Dose Levels

After the MTD of the doublet is confirmed, additional patients will be enrolled at the MTD, with a maximum of 44 patients at that dose (including the 6 patients treated during safety lead-in). After the MTD is confirmed, patients will be eligible for trametinib dose reductions as described in section 6. As described below, early stopping criteria will be used to terminate the trial if there is strong evidence of futility. Using a Simon's 2-stage design (figure 2), we will enroll 29 patients. If there is evidence of 2 or more patients with response, we will enroll the remaining 15. We believe that a larger first stage is justified because an existing PD-L1/MEK trial has shown efficacy (as described in rationale) in a similar mCRC population.

2017-0514
December 19, 2017
Page 27

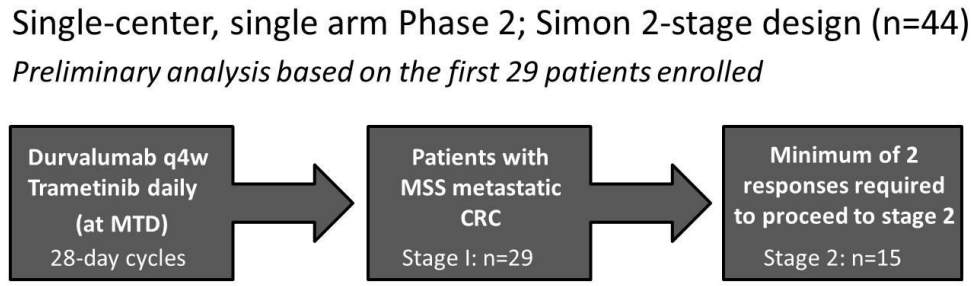

Figure 2: Study design

We will have a lead in period with trametinib alone for 1 weeks (figure 3) for the dual purpose of 1) providing a window to identify toxicities that are related to this agent in monotherapy, and 2) to provide a priming effect before the addition of checkpoint blockade. As described in the background, there is preclinical evidence that better tumor control and survival is achieved with a 1 week trametinib lead in.

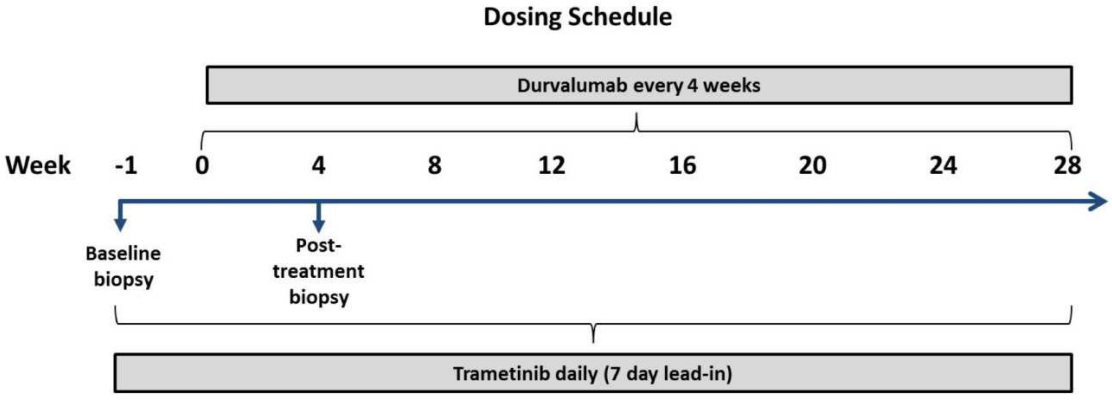

Figure 3: Study dosing schedule

In all patients pre- and on-treatment biopsies will be optional and may become mandatory in order to ensure 15 patients at MTD have paired biopsies. Additionally, peripheral blood will be collected at baseline, day 0, and then approximately every 4 weeks on treatment to examine changes in peripheral immune cells and cytokines. These correlative studies are fundamentally important to identify immunologic changes associated with treatment. A deeper understanding of the cellular and immunologic changes with this combination therapy offers the 1) ability to correlate pre-existing tumor features with response to therapy; 2) ability to quantify changes in the tumor microenvironment with treatment; and 3) opportunity to identify therapeutically relevant difference between patients that may

inform future trials.

Patients will receive restaging imaging every 8 weeks while on therapy, or sooner if deemed appropriate by the investigator. Patients will be eligible to remain on therapy if they demonstrate either response or stable disease as defined by immune-related response criteria. If at the first restaging scan, the patient has progressed, but in the opinion of the investigator shows evidence of clinical benefit and good tolerance of therapy, they may receive an additional cycle of therapy with restaging in 4 weeks.

Study Schematic

5.1.1 Screening visit.
If a patient is thought to be a potential candidate for the trial then he/she can be offered participation and, if agreeable, will undergo screening procedure outlined below from D-21 to D-8.

Table 5.1-1: Screening Procedural Outline

Procedure	Screening Visit From D-21 to D-8	Notes
Eligibility Assessments		
Informed Consent	X	Original IC in screening for protocol participation;
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose.
Medical History	X	
Tumor Tissue Sample	X	Confirm diagnosis of colorectal adenocarcinoma.
MSI Status	X	MSI status must be confirmed; if not available it may be obtained either from archived tissue.
Prior Medications	X	Prior exposure to checkpoint inhibitor therapy excluded
ECOG Performance Status	X	Within 14 days prior to first dose
Safety Assessments		

Table 5.1-1: Screening Procedural Outline		
Procedure	**Screening Visit From D-21 to D-8**	**Notes**
Physical Examination	X	
Vital Signs & Oxygen Saturation	X	Including BP, HR, temperature and oxygen saturation by pulse oximetry (at rest). Obtain vital signs at the screening visit and within 72 hours prior to first dose.
Physical Measurements	X	Height and Weight. Within 14 days prior to first dose
Assessment of Signs and Symptoms	X	Within 14 days prior to first dose
ECG	X	Within 14 days prior to first dose.
Concomitant Medication Collection	X	Within 14 days prior to first dose
Laboratory Tests	X	CBC w/differential and platelet count, Chemistry panel including: LDH, AST, ALT, Alk Phos, T.Bili, Comprehensive metabolic panel, magnesium CEA, amylase, lipase, TSH, Free T4, Free T3, HIV Ab, Hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA), within 14 days prior to starting trametinib
Pregnancy Test (WOCBP only)	X	Serum or urine to be done at screening visit and repeated within 72h of first dose of study therapy
Efficacy Assessment		
Baseline Tumor Imaging Assessment	X	CT of the C/A/P with contrast within 28 days of starting trametinib
Previous collected tumor tissue	X	Request previously collected paraffin embedded tumor tissue
Baseline Tumor biopsy	X	Biopsy of tumor tissue at baseline is optional for all but will be mandatory to ensure 15 patients at MTD have paired biopsies.

5.1.2 Treatments

5.1.2.1 Durvalumab
Durvalumab is a human IgG1κ mAb directed against PD-L1. It will be given at a fixed dose of 1500mg IV over approximately 1 hour on day 1 of each cycle. No premedications are needed. Pharmaceutical details and preparation are provided in section 8. No dose modifications are permitted for this agent. Management of adverse events related to this agent and treatment delays should follow recommendations in section 7.7.

5.1.2.2 Trametinib
Trametinib (GSK/NOVARTIS1120212) is a selective MEK1 and MEK2 inhibitor. It will be taken orally daily at a dose between 1-2mg starting 7 days prior to the first dose of durvalumab. In absence of toxicity, trametinib will be taken daily at approximately the same time each day including on the day of durvalumab infusion. It should be taken 1 hour before or 2 hours after a meal. Do not take a missed dose of trametinib within 12 hours of the next dose of trametinib.

Individual dose reductions for trametinib are permitted. Management of and dose modifications in response to adverse events related to study medications are outlined in section 6 below as described in version 8 of the trametinib IB.

5.1.3 Treatment and Follow Up visits
Once enrolled on trial, subjects will have the following visits/events. The study calendar in section 10 mirrors the events listed below. Please note preferred scans are CT but MRI is allowed as well. In addition, approximately 24 hours of steroid therapy such as prednisone prior to CT scan due to a contrast allergy is allowed.

5.1.3.1 Week -1 (can be up to 7 days prior)
- Special labs for Immunogenicity assessment (up to 8 tubes x 10 mL each)

5.1.3.2 Week 0 (Cycle 1, Day 1)
- Clinic visit with targeted physical examination, vital signs, oxygen saturation, assessment of performance status, and review of concomitant medication
- Assess tolerance of and adherence with trametinib therapy
- Lab tests including CBC with differential and CMP
- Special labs for Immunogenicity assessment (up to 8 tubes x 10 mL each)
- Durvalumab cycle 1 in outpatient infusion suite

5.1.3.3 Week 2 +/- 3 days
- Clinic visit with targeted physical examination, vital signs, oxygen saturation, assessment of performance status, and review of concomitant medication
- Assess tolerance of and adherence with trametinib therapy

- Lab tests including CBC with differential and CMP

5.1.3.4 Week 4 +/- 3 days (+/-7 day window to complete biopsy)

- Clinic visit with targeted physical examination, vital signs, oxygen saturation, assessment of performance status, and review of concomitant medication
- Assess tolerance of and adherence with trametinib therapy
- Lab tests including CBC with differential and CMP, CEA, TSH, and FT4
- Special labs for Immunogenicity assessment (up to 8 tubes x 10 mL each)
- Durvalumab cycle 2 in outpatient infusion suite
- Tumor biopsy in interventional radiology (within +/- 7 days of C2D1). Optional but mandatory for 15 at MTD.

5.1.3.5 Week 6 +/- 3 days

- Clinic visit with targeted physical examination, vital signs, oxygen saturation, assessment of performance status, and review of concomitant medication
- Assess tolerance of and adherence with trametinib therapy
- Lab tests including CBC with differential and CMP

5.1.3.6 Week 8 +/- 3 days (1-week window to complete tests)

- Clinic visit with targeted physical examination, vital signs, oxygen saturation, assessment of performance status, and review of concomitant medication
- Special labs for Immunogenicity assessment (up to 8 tubes x 10ml each)
- Lab tests including CBC with differential, CMP, lipase, amylase, CEA, TSH, and FT4.
- Durvalumab cycle 3 in outpatient infusion suite
- CT scan of the C/A/P with IV contrast
- Tumor measurements

5.1.3.7 Week 12 +/- 3 days (repeating every 4 weeks while on study)

- Clinic visit with targeted physical examination, vital signs, oxygen saturation, assessment of performance status, and review of concomitant medication
- Assess tolerance of and adherence with trametinib therapy
- Lab tests including CBC with differential and CMP
- Special labs for Immunogenicity assessment (up to 8 tubes x 10 mL each) (week 12 only and at progression)
- Durvalumab in outpatient infusion suite

5.1.3.8 Week 16 +/- 7 days(repeating every 8 weeks while on study)

- CT scan of the C/A/P with IV contrast
- Tumor measurements
- CEA, TSH, and FT4

5.2 **Definition of Dose-Limiting Toxicity and Maximum Tolerated Dose:**

5.2.1 *Dose-Limiting Toxicity (DLT*):

DLT is defined as any:

- Any adverse event (AE) of severity grade 3 or 4 (including serious or life-threatening) considered possibly, probably or definitely related to the combination of durvalumab and trametinib (CTCAE v4.0). Any grade 4 immune-realted AE (irAE). The following caveats are listed below:
- If a grade 3 event is felt to be secondary to durvalumab or trametinib alone than this will not be considered a DLT and treatment can be delayed as per 7.7. If toxicity occurs during trametinib lead-in OR is felt to be secondary to trametinib alone, the investigator can dose reduce as per 7.7.
- Only grade 3 lab abnormality that the PI or attending physician feels is clinically significant.
- Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
- Any clinically grade 3 or 4 non-hematologic toxicity as defined in the NCI CTC v4.0, expected and believed to be related to the combination of durvalumab and Trametinib (except nausea and vomiting, diarrhea and electrolyte imbalances responsive to appropriate regimens, alopecia or fatigue lasting less than 7 days).
- Any grade 4 neutropenia (with or without fever and/or sepsis) or thrombocytopenia (with or without bleeding) lasting at least 1 week or longer (as defined by the NCI-CTC v4.0).
- Any of the Grade 4 hematologic adverse events for >5 days.
- Any grade 3 or 4 nausea or vomiting lasting more than 5 days despite anti-emetics regimens or grade 3 or 4 diarrhea refractory to anti-diarrhea medications.
- Any grade ≥ 3 colitis.
- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care.

- Liver transaminase elevation > 8 × ULN or total bilirubin > 5 × ULN.

The definition excludes the following conditions:

- Grade 3 fatigue lasting ≤ 7 days
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc)
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management

5.2.2 *Maximum Tolerated Dose (MTD):*

Maximum Tolerated Dose (MTD) is defined:

- Highest dose level with less than 2 patients with DLT out of at least six patients in the cohort. Management and dose modifications associated with adverse events are outlined in below table.

Number of Patients with DLT* at a Given Dose Level	**Escalation Decision Rule**
1 out of 3	Enter at least 3 more patients at this dose level. If 0 of these 3 patients experience DLT, continue enrollment at current dose level dose level. If 1 or more of this group suffer DLT this dose is declared the maximally administered dose. Three additional patients will be entered at the next lowest dose level if 3 patients were treated

	previously at that dose.
≥2 out of 3	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three additional patients will be entered at the next lowest dose level if 3 or fewer patients were treated previously at that dose.
< =1 out of 6 at highest dose level below the maximally administered dose	This is generally the MTD. At least 6 patients must be entered at the MTD.

***The time window for DLT evaluation among the first 6 patients is 28 days (one cycle*)**

All patients will be treated at the highest current dose level. All enrolled participants will be considered in the DLT analysis. If patients experiencing DLTs related to trametinib, they can continue combination therapy at the next lowest dose as described in section 6.

5.3 General Concomitant Medication and Supportive Care Guidelines

Concommitant medications will be recorded in the medical record only.

Table 1 Supportive Medications

Supportive medication/class of drug:	**Usage:**
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all subjects
Inactivated viruses, such as those in the influenza vaccine	Permitted

Excluded concomitant medications

Table 1. Prohibited Concomitant Medications

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy])
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding <<10 mg/day>> of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions: · Use of immunosuppressive medications for the management of IP-related AEs, · Use in patients with contrast allergies. · In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of fixed during the study.
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)

Prohibited medication/class of drug:	**Usage:**
EGFR TKIs <<unless the study is assessing the combination of an EGFR TKI and durvalumab>>	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Per investigator discretion but in general not recommend to be given concomitantly.

Durvalumab and trametinib have been studied in ongoing trial in metastatic melanoma. Among 20 metastatic melanoma patients treated with the combination, all experienced AEs of at least grade 1 or higher [Ribas et al, ASCO AM 2015]. A dose-limiting toxicity of reversible choroidal effusion was observed in one patient. The most common AEs (by percent patients) were diarrhea (50%), rash (35%), fatigue (30%), and folliculitis (25%).

5.4 **Restrictions for Patients on Study**

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

Female patient of child-bearing potential:
– Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Table 5.) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of durvalumab + any drug combination therapy or 90 days after the last dose of durvalumab monotherapy. Non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female subjects should also refrain from breastfeeding throughout this period.

Male subjects with a female partner of childbearing potential:
– Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 180 days after receipt of the final dose of durvalumab + any drug combination therapy or 90 days after receipt of the final dose of durvalumab monotherapy. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male subjects should refrain from sperm donation throughout this period.

– Female partners (of childbearing potential) of male subjects must also use a highly effective method of contraception throughout this period (Table 5.).

Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal

treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Table 5.. Note that some contraception methods are not considered highly effective (eg male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 5.2. Highly Effective Methods of Contraception (<1% Failure Rate)

• Barrier/Intrauterine methods	• Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a]	• Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplan® • Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing® • Injection: Medroxyprogesterone injection: e.g. Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra® • Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based

[a] This is also considered a hormonal method

Blood donation

Subjects should not donate blood while participating in this study, or for at least 90 days following the last infusion of durvalumab or tremelimumab or 90 days after receipt of the final dose of durvalumab.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies: disease progression, intercurrent illness that prevents further administration of therapy, unacceptable adverse events, patient decides to withdraw from study, or general or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgement of the investigator.

5.6 Duration of Follow Up

Patients will be followed for 1.5 years after completion of active treatment from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6. DOSING DELAYS/DOSE MODIFICATIONS

Adjustments for Durvalumab and Trametinib will follow the guidelines and recommendations noted below. Based on the mechanism of action of Durvalumab and Trametinib leading to T-cell activation and proliferation, the occurrence of irAEs that are either overlapping or greater than each of these drugs when used as monotherapy is possible though considered unlikely. Adjustments can be made to both drugs or each drug independently if a toxicity is felt to be specifically related to one of the drugs. For specific non-immune related toxicities that are expected with trametinib alone, trametinib modification should follow table 6.3. If one study agent is discontinued due to toxicity then the patient may continue on protocol with the other agent if it is felt in the patients best interest by the treating physician. The decision to dose adjustment should be based upon investigator determined attribution as at least possibly related to trametinib.

Potential irAEs may include[29, 32, 33, 57]:

- Gastrointestinal events including colitis, intestinal perforation, abdominal pain, dehydration, nausea and vomiting, and decreased appetite (anorexia)
- Dermatitis including urticaria, skin exfoliation, and dry skin
- Endocrinopathies including hypophysitis, adrenal insufficiency, and hyper and hypothyroidism
- Hepatitis including autoimmune hepatitis, and increased serum alanine aminotransferase and aspartate aminotransferase
- Pancreatitis including autoimmune pancreatitis, and lipase and amylase elevation

- Respiratory tract events including pneumonitis and interstitial lung disease
- Nervous system events including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and myasthenia gravis (the latter reported with combination of tremelimumab and Durvalumab)
- Cytopenias including thrombocytopenia, anemia and neutropenia
- Infusion-related reactions, anaphylaxis, and serious allergic reactions
- Headache, fatigue, and pyrexia
- Serious infections
- Immune complex disease.

Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (eg, infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, pneumonitis, dermatitis, hepatitis, neuropathy, and endocrinopathy. In addition to the treatment modifications shown in Table 6.4/6.5 it is recommended that management of irAEs follow the guidelines outlined for ipilimumab [58]. These guidelines recommend the following:

1. Subjects should be evaluated to identify any alternative etiology.
2. In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered to be immune-related.
3. Symptomatic and topical therapy should be considered for low-grade events.
4. Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
5. More potent immunosuppressives should be considered for events not responding to systemic steroids (eg, infliximab, mycophenolate, etc).

All toxicities will be graded according to NCI CTCAEv4.03. In case of doubt, the investigator should consult with the AstraZeneca / MedImmune .If the investigator has any question in regards to an AE being an irAE, the investigator should immediately contact the AstraZeneca / MedImmune . Treatment modifications will not be required for AEs that are clearly not attributed to Durvalumab or Trametinib (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant.

Dose reductions of Durvalumab are not permitted. Dose reductions of trametinib are permitted as in table 6.2

Treatment modifications may be required for Durvalumab and Trametinib in the event of treatment-related toxicity. General guidelines regarding treatment modification are provided in the following tables.
-Table 6.1 Recommended dose level reductions for Trametinib
-Table 6.2 **Trametinib** specific dose modification schedule

-Table 6.3 Predominantly trametinib specific toxicity: dose modification schedule for **trametinib and durvalumab**
-Table 6.4 **Durvalumab** dose modification schedule
-Table 6.5 Adverse events of special interest (AESI): **durvalumab and trametinib** dose adjustment schedule.

Table 6.1 Recommended dose level reductions for Trametinib

Dose Level	Trametinib Dose
Starting dose	2 mg QD
1st dose reduction	1.5 mg QD
2nd dose reduction	1 mg QD
QD = Once daily	
Refer to the [Dabrafenib (GSK2118436) Monotherapy and Dabrafenib+Trametinib (GSK1120212) Combination Therapy Investigator's Brochure] for dabrafenib dosing instructions	
Dose adjustment for trametinib, whether used as monotherapy or in combination with dabrafenib, below 1 mg QD is not recommended.	

Table 6.2 Trametinib dose modification schedule

Grade (CTC-AE)*	**Dose Modifications**
Grade 1 or Grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is grade 0-1and reduce by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until Grade 0 to 1 and reduce by one dose level when resuming therapy.
* The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)	

Table 6.3 Predominantly trametinib specific toxicity: dose modification schedule for trametinib and durvalumab

CTCAE v4.0 **Adverse Event**	**Trametinib**	**Durvalumab**
Cardiac Disorders		
LV systolic dysfunction	*Also refer to "Decreased ejection fraction" in Investigations*	
Grade 3	Permanently discontinue trametinib; consider evaluation by a cardiologist.	Continue durvalumab at same dose level
Grade 4	Continue to monitor the LVEF at 2 weeks, 4 weeks, and then every 4 weeks through week 16 or until resolution	

CTCAE v4.0 Adverse Event	Trametinib	Durvalumab
Hypertension Grade 1	– Continue trametinib at same dose level.	Continue durvalumab at same dose level
Grade 2	• Continue trametinib at the current dose • Adjust current or initiate new antihypertensive medication • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled BP • If BP is not well controlled within 2 weeks, consider referral to a specialist and manage as for Grade 3.	Continue durvalumab at same dose level
Grade 3	• If symptomatic, interrupt trametinib. If asymptomatic, consider interrupting trametinib if clinically indicated • Adjust current or initiate new antihypertensive medication(s) • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP • If symptomatic or persistent Grade 3 hypertension despite antihypertensive medications and dose reduction of trametinib, recommend referral to a specialist for further evaluation and follow-up • Once BP is well controlled, restart trametinib **reduced by one dose level**	Continue durvalumab at same dose level
Grade 4	Permanently discontinue trametinib	Continue durvalumab at same dose level
ECG QT corrected interval prolonged Grade 1	Continue trametinib at same dose level.	Continue durvalumab at same dose level.
Grade 2		
Grade 3	*Note regarding Grade 3: If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period and average the QTc values of the 3 ECGs. Based on the average QTc value of triplicate ECGs (confirmed via manual over-read), modify therapy as outlined below.*	
	• **If QTcf > 501 msec or uncorrected QT**	

CTCAE v4.0 Adverse Event	Trametinib	Durvalumab
	> 600 msec or QTcf > 530 msec for subjects with bundle branch block, interrupt therapy. • If the QTc prolongation resolves to ≤ 480 msec, trametinib therapy may be resumed at the same dose level, if the investigator and AstraZeneca / MedImmune agree that the patient could benefit from further treatment. • If the event recurs, permanently discontinue trametinib.	Continue durvalumab at same dose level.
Grade 4	Permanently discontinue trametinib.	Permanently discontinue durvalumab.
Ejection fraction ↓	*For instructions for patients with symptomatic ↓ in LVEF,* *refer to "Left ventricular systolic dysfunction" in Cardiac Disorders*	
Grade 2	• Interrupt trametinib and repeat ECHO/MUGA within 2 weeks. If not recovered, repeat again in 2 weeks. • If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline) • Consult with the AstraZeneca / MedImmune and request approval to restart trametinib. • Restart treatment with trametinib reduced dose by one dose level • Repeat ECHO/MUGA 2, 4, 8, and 12 weeks after restart; continue in intervals of 12 weeks thereafter. • If LVEF remains stable for 4 weeks after restarting trametinib, may request approval from AstraZeneca / MedImmune to reescalate to previous dose level. • If LVEF **does not recover** within 4 weeks • Consult with cardiologist • **Permanently discontinue trametinib** • **Report as SAE** • Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution • Consult with AstraZeneca / MedImmune	Continue durvalumab at same dose level.

CTCAE v4.0 Adverse Event	Trametinib	Durvalumab
Grade 3	If symptomatic, permanently discontinue trametinib. If asymptomatic, follow instructions for Grade 2 ↓ in ejection fraction.	Continue durvalumab at same dose level.
Grade 4	Permanently discontinue trametinib.	Permanently discontinue durvalumab.
Eye Disorders		
Retinopathy and Other Eye Disorders Grade 1	If visual changes are clearly not due to retinal or retinal vein abnormalities or are clearly unrelated to study drug (e.g., allergic conjunctivitis), continue trametinib with close observation. If etiology is unclear, immediately refer patient for ophthalmic exam; if dilated fundus exam cannot be performed within 7 days, interrupt trametinib until exam is performed. If RPED or RVO excluded, continue (or restart) trametinib at same dose level. If RVO diagnosed, permanently discontinue trametinib. If RPED suspected or diagnosed and asymptomatic, continue trametinib with monthly retinal exam until resolution. If symptomatic or grade 1 RPED worsens, interrupt trametinib, with monthly retinal exam until improved to ≤ Grade 1 and restart with reduction by one dose level.	Continue durvalumab at same dose level
Grade 2	Immediately interrupt trametinib therapy and refer patient for ophthalmic exam. If RPED or RVO excluded, restart trametinib at same dose level. If RVO diagnosed, permanently discontinue trametinib.	Continue durvalumab at same dose level OR interrupt therapy until eye disorder is stable; then resume therapy at same dose level.
Grade 3	If RPED diagnosed and asymptomatic, continue trametinib with monthly retinal exam until resolution. If symptomatic or grade 1 RPED worsens, interrupt trametinib, with monthly retinal exam until improved to ≤ Grade 1 and restart at reduction by one dose level.	Interrupt therapy until eye disorder is stable. If found to have inflammatory condition, treat with steroids and permanently discontinue durvalumab.
Grade 4	• Immediately interrupt trametinib therapy and refer patient for ophthalmic exam. – If RPED or RVO excluded, consider restarting trametinib at same or reduced dose level after discussion with AstraZeneca / MedImmune .	

CTCAE v4.0 Adverse Event	Trametinib	Durvalumab
	– If RVO or RPED diagnosed, permanently discontinue trametinib.	
Skin and Subcutaneous Tissue Disorders		
Rash Grade 1 (Mild)	• Continue trametinib at current dose • If rash does not recover to baseline within 2 weeks despite best supportive care, reduce trametinib by one dose level	Continue durvalumab at current dose.
Grade 2 (Moderate)	• Reduce trametinib by one dose level • If rash recovers to ≤grade 1 within 2 weeks, increase dose to previous dose level • If no recovery to ≤grade 1 within 2 weeks, interrupt trametinib until recovery to ≤grade 1, and then restart trametinib at reduced dose level	Continue durvalumab at current dose. Consider skin biopsy if persistent for >2 weeks or recurs
Grade 3 (Severe)	• Interrupt trametinib until rash recovers to grade ≤1 • Restart with trametinib reduced by one dose level • If no recovery to grade ≤2 within 4 weeks, permanently discontinue trametinib	• Hold durvalumab until rash recovers to grade ≤2. If rash recovers to ≤grade 2, restart durvalumab. • If grade 3 rash occurs a second time, withhold durvalumab until rash recovers to grade ≤2. If rash recovers to ≤grade 2, restart durvalumab. • If grade 3 rash occurs a third time, permanently discontinue durvalumab. • Consider consult dermatology • Consider promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent if believed immune-related rash • Consider skin biopsy (preferably more than 1) as clinically feasible. - If felt to be immune related discuss with Principal investigator **IF THERE IS ANY BULLOUS FORMATION, THE PRINCIPAL INVESTIGATOR SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED****

CTCAE v4.0 Adverse Event	Trametinib	Durvalumab
Grade 4		Permanently discontinue durvalumab. • Consult dermatology • Consider promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent if believed immune-related rash • Consider skin biopsy (preferably more than 1) as clinically feasible. - If felt to be immune related discuss with Principal investigator **IF THERE IS ANY BULLOUS FORMATION, THE PRINCIPAL INVESTIGATOR SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED****

Table 6.4 **Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy) 1 November 2017 Version**

Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤10 mg/day or equivalent. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen.	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: – It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted specifically in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology – (e.g., disease progression, concomitant medications, and infections).) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Some events with high likelihood for morbidity and/or mortality – e.g., myo-carditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Discuss these eventsConsider, as necessary, discussing with the study physician, and promptly pursue subspecialisty consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper).

2017-0514
December 19, 2017
Page 48

Table 6.4 **Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy) 1 November 2017 Version**

Dose Modifications	Toxicity Management
Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	– More potent immunosuppressives such as TNF inhibitors (eg, infliximab) (also refer to the individual sections of the irAE for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (eg, inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit/risk analysis for that patient.

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; IV intravenous; NCI National Cancer Institute; PO By mouth.

2017-0514
December 19, 2017
Page 49

Pediatric Considerations

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks** after last dose of study drug/study regimen	– All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for dosing of steroids (i.e., mg/kg/day) and for IV IG and plasmapheresis that are provided for adult patients should also be used for pediatric patients. – The infliximab 5 mg/kg IV dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For dosing in children younger than 6 years old, consult with a pediatric specialist. – For pediatric dosing of mycophenolate mofetil, consult with a pediatric specialist. – With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

2017-0514
December 19, 2017
Page 50

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	General Guidance	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider pulmonary and infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is

2017-0514
December 19, 2017
Page 51

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[a] – Consider pulmonary and infectious disease consult. – Consider, as necessary, discussing with principal investigator.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [eg, tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain pulmonary and infectious disease consult. – Hospitalize the patient. – Supportive care (eg, oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patients is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation).[a]
Diarrhea/Colitis	**Any Grade**	General Guidance	**For Any Grade:**

2017-0514
December 19, 2017
Page 52

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			– Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	(Colitis: abdominal pain; mucus or blood in stool)	• If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	– Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeksa. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consult principal investigator if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: stool frequency of ≥7 over baseline per day;	Grade 3 Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (eg infliximab at 5 mg/kg

2017-0514
December 19, 2017
Page 54

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 4: diarrhea life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medi-cal intervention indi-cated, peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)	Grade 4 Permanently discontinue study drug/study regimen.	once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Grade**	General Guidance	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications,).
	Grade 1 AST or ALT > to 3 × ULN and/or TB > to 1.5 × ULN)	No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT > 3 to 5 ×	• Hold study drug/study regimen dose until Grade 2 resolution to	**For Grade 2:** – Regular and frequent checking of LFTs (eg, every 1 to 2 days)

2017-0514
December 19, 2017
Page 55

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	ULN and/or TB >1.5 to 3.0 × ULN)	Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, consider as necessary, discussing with principal investigator. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e. mycophenolate mofetil)[a] Discuss with principal investigator if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: AST or ALT >5 to 20 × ULN and/or TB >3.0 to 10 × ULN) (Grade 4: AST or ALT >20 × ULN and/or TB >10 × ULN)	**For Grade 3:** For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e mycophenolate mofetil). Discuss with principal investigator if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging

2017-0514
December 19, 2017
Page 56

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (ie, elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB.

2017-0514
December 19, 2017
Page 57

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
immune-related hepatitis.			– Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
	Grade 1 (Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline)	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as Grade 2 event. For all grades, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	

2017-0514
December 19, 2017
Page 58

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 2 (Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline) (Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	Grade 3 (Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline)	• Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or	**For Grade 3:** – Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy.

2017-0514
December 19, 2017
Page 59

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	(Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)	baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	– Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 4 (Isolated AST or ALT >20×ULN, whether normal or elevated at baseline)	Permanently discontinue study drug/study regimen.	**For Grade 4:** **Same as above** **(except would recommend obtaining liver biopsy early)**
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	General Guidance	**For Any Grade:** – Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or

2017-0514
December 19, 2017
Page 60

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression or infections). – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum creatinine > 1 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade	General Guidance	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE PRINCIPAL

2017-0514
December 19, 2017
Page 62

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	depending on type of skin rash)		INVESTIGATOR SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with principal investigator and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	– Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Consider, as necessary, discussing with principal investigator.
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with principal investigator. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and realted labs (e.g., blood glucose and ketone levels, HgA1c). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as

2017-0514
December 19, 2017
Page 64

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus,, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after	**For Grade 2 (including those with symptomatic endocrinopathy):** – . – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For patients with abnormal endocrine work up, except for those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (eg, 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with

2017-0514
December 19, 2017
Page 65

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	relevant hormone replacement (eg, levothyroxine, hydrocortisone, or sex hormones). – – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus,, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones) – For adrenal crisis, severe dehydration, hypotension, or shock,

2017-0514
December 19, 2017
Page 66

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. Doses of prednisone are ≤10 mg/day or equivalent.	immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once the patients on steroids are improving, gradually taper immunosuppressive steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated. – Discuss with principal investigator.
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications.	**For Grade 1:**

2017-0514
December 19, 2017
Page 67

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			– See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** – Consider, as necessary, discussing with the principal investigator. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (eg, IV IG).
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study	**For Grade 3 or 4:** – Consider, as necessary, discussing with principal investigator. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (eg, IV IG). – Once stable, gradually taper steroids over ≥28 days.

2017-0514
December 19, 2017
Page 68

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		drug/study regimen.	
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	General Guidance	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and “repetitive stimulation” if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 1	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the principal investigator. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Consider, as necessary, discussing with the principal investigator. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition

2017-0514
December 19, 2017
Page 70

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* ○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Consider, as necessary, discussing with principal investigator. – Recommend hospitalization. – Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* ○ Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. ○ If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:*

2017-0514
December 19, 2017
Page 71

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)

2017-0514
December 19, 2017
Page 72

Grade 1 (asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.
Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles

		including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.

2017-0514
December 19, 2017
Page 74

Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is

For Grade 4: - Permanently discontinue study drug/study regimen.	important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]	[a]

ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.

[b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PCP ; PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Infusion-related Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** – Manage per institutional standard at the discretion of investigator. – Monitor patients for signs and symptoms of infusion-related reactions (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. – Consider premedication per institutional standard prior to subsequent doses. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Manage severe infusion-related reactions per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM Intramuscular; IV Intravenous; NCI National Cancer Institute.

Non-immune-mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (ie, events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the MedImmune (AstraZeneca).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Principal investigator."

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

Table 6.5 Adverse events of special interest (AESI): durvalumab and trametinib dose adjustment schedule.

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Pneumonitis/ILD	Grade of Pneumonitis (CTCAE version 4.03)	Any Grade	– Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.
	Grade 1 (Asymptomatic, clinical or diagnostic observations only, intervention not indicated)	No dose modification required. However, consider holding **trametinib and durvalumab** dosing as clinically appropriate and during diagnostic work-up for other etiologies	For Grade 1 (Radiographic Changes Only) – Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated. – Consider pulmonary and infectious disease consult.
	Grade 2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	Hold **trametinib and durvalumab** dose until grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then the decision to reinitiate study drug/regimen at next scheduled	For Grade 2 (Mild to Moderate New Symptoms) – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1-2mg/kg/day or IV equivalent) Reimaging as clinically indicated – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
		treatment date will be based upon treating physician's clinical judgment. **durvalumab** treatment can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper When recovered, restart **trametinib** by one dose level. May consider reescalation to previous dose level after 4 weeks after discussion with AstraZeneca / MedImmune .	– If still no improvement within 3-5 days despite IV methylprednisone at 2-4/g/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab – Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[121] – Consider pulmonary and infectious disease consult – Consider as necessary discussing with principal investigator
	Grade 3 or 4 (Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated; Grade 4: life threatening respiratory compromise , urgent intervention indicated [e.g.	Permanently discontinue **trametinib and durvalumab**	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Obtain pulmonary and infectious disease consult – Hospitalize the patient – Supportive Care (oxygen, etc.) – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2

1 ASCO Educational Book 2015. Michael Postow MD. "Managing Immune Checkpoint Blocking Antibody Side Effects"

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	tracheostomy or intubation])		weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[3]
Diarrhea/ Enterocolitis	Grade of Diarrhea (CTCAE version 4.03)	Any Grade	- Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus) - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections including testing for clostridium difficile toxin, etc.) - Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event - Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1 diarrhea (stool frequency of <4 over baseline per day)	No dose modification	For Grade 1 diarrhea : - Close monitoring for worsening symptoms - Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment.
	Grade 2 diarrhea (stool	Hold **trametinib and durvalumab** until resolution to ≤ Grade	For Grade 2 diarrhea:

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	frequency of 4-6 over baseline per day)	1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date Study **trametinib and durvalumab** can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper	– Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide – Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. – If still no improvement within 3-5 days despite 2-4mg/kg IV methylprednisolone, promptly start immunosuppressives such as (infliximab at 5mg/kg once every 2 weeks[2]). . **Caution**: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab – Consult principal investigator if no resolution to ≤ Grade 1 in 3-4 days – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

2 ASCO Educational Book 2015 Michael Postow MD "Managing Immune Checkpoint Blocking Antibody Side Effects

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4 diarrhea (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)	Interrupt both therapies until symptoms resolve to ≤ Grade 1 or baseline. Resume therapy with a ↓ of one dose level of **trametinib**. If immune related diarrhea, permanently discontinue **durvalumab.**	For Grade 3 or 4 diarrhea: - Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent - Monitor stool frequency and volume and maintain hydration - Urgent GI consult and imaging and/or colonoscopy as appropriate - If still no improvement within 3-5 days of IV methylprednisolone 2 to 4mg/kg/day or equivalent, promptly start further immunosuppressives (e.g. infliximab at 5mg/kg once every 2 weeks). - Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
Hepatitis (Elevated LFTs) **Infliximab should not be used for management of Immune Related Hepatitis**	Grade of Liver Function Test Elevation (CTCAE version 4.03) Any Grade Grade 1 (AST or ALT > ULN to 3 times ULN and/or TB > ULN to 1.5 times ULN)	No dose modification If it worsens, treat as Grade 2 event	- Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin - Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications) For Grade 1 AST or ALT and/or TB elevation - Continue LFT monitoring per protocol

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 2 (AST or ALT > 3 to 5 times ULN and/or TB >1.5-3.0 times ULN)	Hold Study **trametinib and durvalumab** dose until grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If improves to baseline then treat at next scheduled treatment date Study **trametinib and durvalumab** can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper	For Grade 2 AST or ALT and or TB elevation : – Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved. – If no resolution to ≤ Grade 1 in 1-2 days, discuss with principal investigator. – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2mg/kg/day or IV equivalent. – If still no improvement within 3-5 days despite 1-2mg/kg/day of prednisone or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. – If still no improvement within 3-5 days despite 2-4mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil)[3] . Discuss with principal investigator if mycophenolate mofetil is not available. **Infliximab should NOT be used**. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 (AST or ALT >5-20 times ULN and/or TB > 3.0-10 times ULN	For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × ULN -Hold **trametinib and durvalumab** dose until resolution to ≤ Grade 1 or	For Grade 3 or 4 AST or ALT and/or TB elevation: – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent – If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent , promptly start treatment

3 ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" , by Michael Postow MD

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
		baseline -Resume **trametinib and durvalumab** administration at the next scheduled dose if elevations downgrade ≤ Grade 1 or baseline within 14 days Permanently discontinue **trametinib and durvalumab** if the elevations do not downgrade to ≤ Grade 1 or baseline within 14 days For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue **trametinib and durvalumab** Permanently discontinue **trametinib and durvalumab** for any case meeting Hy's law criteria (ALT > 3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (i.e. elevated alkaline P04) and in the absence of any alternative cause[4]	with immunosuppressive therapy (mycophenolate mofetil) Discuss with principal investigator if mycophenolate is not available. **Infliximab should NOT be used.** - Hepatology consult, abdominal workup, and imaging as appropriate. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 4 (AST or ALT > 20 times ULN and/or TB > 10 times ULN)	Permanently discontinue **trametinib and durvalumab**	
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)	Grade of Elevated Serum Creatinine (CTCAE version 4.03) Any Grade		– Consult with Nephrologist – Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.) – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.) – Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2) , in order to prevent potential progression to higher grade event
	Grade 1 [Serum Creatinine > 1-1.5X baseline; > ULN to 1.5X ULN]	No dose modification	For Grade 1 elevated creatinine: – Monitor serum creatinine weekly and any accompanying symptom • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If it worsens, depending on the severity , treat as Grade 2 or Grade 3 or 4 - Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 2 [Serum Creatinine> 1.5-3.0X baseline; >1.5X-3.0XULN]	Hold **trametinib and durvalumab** until resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date **trametinib and durvalumab** can be resumed at the next scheduled dose once event stabilizes to grade ≤1 for 5-7 days have passed after completion of steroid taper	For Grade 2 elevated creatinine: – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. – Carefully monitor serum creatinine every 2-3 days and as clinically warranted – Consult Nephrologist and consider renal biopsy if clinically indicated – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/kg/day started. – Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: Serum Creatinine > 3.0 X baseline; >3.0-6.0 X ULN Grade 4: Serum Creatinine >	Permanently discontinue **trametinib and durvalumab**	– Carefully monitor serum creatinine on daily basis – Consult Nephrologist and consider renal biopsy if clinically indicated – Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	6.0 X ULN)		treatment with IV methylprednisolone 2-4mg/kg/day started. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]
	Grade 4	Permanently discontinue **trametinib and durvalumab**	
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)	Any Grade (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity)		– Consult Endocrinologist – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.) – Monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine labs depending on suspected endocrinopathy. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 1 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade 1)	No dose modification	For Grade 1: (including those with asymptomatic TSH elevation) – Monitor patient with appropriate endocrine function tests – If TSH < 0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 2)	For Grade 2 endocrinopathy other than hypothyroidism, hold **durvalumab** dose until subject is clinically stable • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date Study **durvalumab** can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with **durvalumab** on the following conditions: 1) the	For Grade 2: (including those with symptomatic endocrinopathy) – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids – Initiate hormone replacement as needed for management – Evaluate endocrine function, and as clinically indicated, consider pituitary scan – For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term, corticosteroids (e.g., 1-2mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. Levothyroxine, hydrocortisone, or sex hormones). - – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
		event stabilizes and is controlled ,2) the patient is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.	
	Grade 3 or 4 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 3 or 4)	For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold **trametinib and durvalumab** until endocrinopathy symptom(s) are controlled Resume **trametinib and durvalumab** n if controlled at the next scheduled dose Study **trametinib and durvalumab** can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper	For Grade 3 or 4: - Consult endocrinologist - Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids - Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent - Administer hormone replacement therapy as necessary. - For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity - Once improving, gradually taper immunosuppressive steroids over ≥4 weeks and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) - Discuss with principal investigator

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Immune mediated Neurotoxicity (to include but not limited to limbic encephalitis . autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	Any Grade		– Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.) – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness) – Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations) – Symptomatic treatment with neurological consult as appropriate
	Grade 1	No dose modifications	See “Any Grade” recommendations above.
	Grade 2	• For acute motor neuropathies or neurotoxicity, hold **durvalumab** until resolution to ≤ Grade 1 • For sensory neuropathy/neuropathic pain, consider holding **durvalumab** dose until resolution to ≤ Grade 1. • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next	– Discuss with the principal investigator – Obtain Neurology Consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) – Promptly start systemic steroids prednisone 1-2mg/kg/day or IV equivalent – If no improvement within 3-5 days despite 1-2mg/kg/day prednisone or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG)

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
		scheduled treatment date **durvalumab** can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper	
	Grade 3	• Hold **trametinib and durvalumab** until resolution to ≤ Grade 1 • Permanently discontinue **trametinib and durvalumab** if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days.	For Grade 3 or 4: – Discuss with principal investigator – Obtain Neurology Consult – Consider hospitalization – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG) Once stable, gradually taper steroids over ≥4 weeks
	Grade 4	• Permanently discontinue **trametinib and durvalumab**	For Grade 3 or 4: – Discuss with principal investigator – Obtain Neurology Consult – Consider hospitalization – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG) – Once stable, gradually taper steroids over ≥4 weeks
		• Any Grade	

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			– The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation – Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			IVIG and followed by plasmapheresis if not responsive to IVIG
Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis	Grade 1	No dose modification	– Discuss with the principal investigator – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above Obtain a neurology consult unless the symptoms are very minor and stable
	Grade 2	Hold study **trametinib and durvalumab** dose until resolution to ≤ Grade 1 Permanently discontinue **trametinib and durvalumab** if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	Grade 2 – Discuss with the principal investigator – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above – Obtain a Neurology Consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) ***MYASTHENIA GRAVIS*** – Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. – Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. – If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. ***GUILLAIN-BARRE:***

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			– Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
	Grade 3	Hold **trametinib and durvalumab** dose until resolution to ≤ Grade 1 Permanently discontinue **trametinib and durvalumab** if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	For severe or life threatening (Grade 3 or 4) events: – Discuss with principal investigator – Recommend hospitalization – Monitor symptoms and obtain neurological consult ***MYASTHENIA GRAVIS*** – Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. – Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. – If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. ***GUILLAIN-BARRE*:** – Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
	Grade 4	Permanently discontinue **trametinib and durvalumab**	For severe or life threatening (Grade 3 or 4) events: – Discuss with principal investigator

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			– Recommend hospitalization – Monitor symptoms and obtain neurological consult ***MYASTHENIA GRAVIS*** – Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. – Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. – If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. ***GUILLAIN-BARRE*:** – Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG

DURVALUMAB Infusion-Related Reactions		
Severity Grade	**Dose Modifications**	**Toxicity Management**
Any Grade		– Management per institutional standard at the discretion of investigator – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
Grade 1	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event	For Grade 1 or Grade 2: – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator – Consider premedication per institutional standard prior to subsequent doses
Grade 2	The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event Subsequent infusions may be given at 50% of the initial infusion rate	
Grade 3/4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)

6.6 **Permanent discontinuation of Durvalumab therapy**

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1. An individual patient will not receive any further durvalumab monotherapy if their weight falls to 30kg or less

2. Withdrawal of consent or lost to follow-up
3. Adverse event that, in the opinion of the investigator or the MedImmune (AstraZeneca), contraindicates further dosing
4. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk
5. Pregnancy or intent to become pregnant
6. Any AE that meets criteria for discontinuation as defined in Section 6.6
7. Dose-limiting toxicity (See Section 6.5 for definition of DLT) if applicable
8. Grade ≥ 3 infusion reaction
9. Subject noncompliance that, in the opinion of the investigator, warrants withdrawal; eg, refusal to adhere to scheduled visits
10. Initiation of alternative anticancer therapy including another investigational agent
11. Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with durvalumab
12. Subjects who are permanently discontinued from receiving investigational product will be followed for safety, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled I another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative

Withdrawal of consent

Subjects are free to withdraw from the study at any time (IP and assessments) without prejudice to further treatment.

Subjects who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- all further participation in the study including any further follow up (eg, survival contact telephone calls)

- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 **Definition of Adverse Events**

The International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

> Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore 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.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cells increased). Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product. Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment (i.e. a research tumor biopsy) should be recorded as an AE or SAE.

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

· Is accompanied by clinical symptoms
· Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
· Results in a medical intervention (e.g., potassium supplementation for hypokalemia)

or a change in concomitant therapy

· Is clinically significant in the investigator's judgment

Certain abnormal values may not qualify as adverse events. It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

7.2 **Definition of Adverse Events of Special Interest**

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator.. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the Principal investigator.

AESIs observed with durvalumab ± tremelimumab include:

- Pneumonitis / ILD
- hepatitis / transaminase increases
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Endocrinopathies (i.e. events of hypophysitis, hypopituitarism adrenal insufficiency, diabetes insipidus, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis/serum lipase and amylases increases
- Other inflammatory responses that are rare with a potential immune-mediated aetiology include, but are not limited to, myocarditis, pericarditis, and uveitis and other events involving the eye, skin, haematological and rheumatological events.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator's Brochures. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (see Section 6). These guidelines have been prepared by the MedImmune (AstraZeneca) and Novartis to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines

apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

Further information on these risks (eg. presenting symptoms) can be found in the current version of the durvalumab Investigator Brochure.

If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines will be applied. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage.

In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation
The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination
  - Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.
- SpO2
  - Saturation of peripheral oxygen (SpO2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    (i) ILD Markers (KL-6, SP-D) and β-D-glucan
    (ii) Tumour markers: Particular tumour markers which are related to disease progression.

Additional Clinical chemistry: CRP, LDH

7.2.1 **Hepatic Function Abnormality**
Hepatic function abnormality meeting the definition of Hy's law (ie, any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN) is considered an AESI. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up

investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (eg, cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Guidelines for management of subjects with hepatic function abnormality are outlined in table 6.5.

7.2.2 **Pneumonitis**
Adverse events of pneumonitis are also of interest, as pneumonitis has been observed with anti-PD-1 mAbs (but not with anti-PD-L1 mAbs). Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended. Guidelines for management of subjects with pneumonitis are outlined in Section 7.7.

7.2.3 **Infusion Reactions**
Adverse events of infusion reactions (also termed infusion-related reactions) are of special interest and are defined, for the purpose of this protocol, as all AEs occurring from the start of the study treatment infusion up to 48 hours after the infusion start time. For all infusion reactions, the eCRF should be completed as instructed in Section, 7.4 and all SAEs should be reported to MedImmune Patient Safety as described in Section 7.5.

7.2.4 **Hypersensitivity Reactions**
Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy [33]. As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (immunoglobulin E-mediated) and anaphylactoid reactions against the mAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, urticaria, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness. Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are outlined in Section 7.7.

7.2.5 **Gastrointestinal Disorders**
Diarrhea/colitis is the most commonly observed treatment emergent SAE. In rare cases colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Diarrhea/colitis in subjects receiving durvalumab should be managed as outlined in Section 7.7.

7.3 **Recording of Adverse Events**

AEs and SAEs will be collected from the time of the patient signing the informed consent form until the follow-up period is completed (90 days after the last dose of durvalumab ±tremelimumab). If an event that starts post the defined safety follow up period noted above is considered to be due to a late onset toxicity to study drug then it should be reported as an AE or SAE as applicable.

During the course of the study, all AEs and SAEs should be proactively followed up for each patient for as long as the event is ongoing. Every effort should be made to obtain a resolution for all events, even if the events continue after the patient has discontinued study drug or the study has completed.

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF (Protocol Data Management System/Clinical Oncology Research System - PDMS/CORe). AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

See Section 7.2 for the definition of SAEs. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form. Infusion of biological products is commonly associated with infusion-related reactions.

The following variables will be collected for each AE:
- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Outcome

In addition, the following variables will be collected for SAEs:
- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)

- Causality assessment in relation to other medication
- Description of the SAE

The grading scales found in the revised NCI CTCAE version 4.03 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

Anaphylaxis and infusion-related reactions have some common manifestations and may be difficult to distinguish from each other. Infusion-related reactions are commonly observed during or shortly after the first time exposure to therapeutic mAbs delivered through intravenous infusion. These reactions are less common following subsequent exposures. Unlike infusion-related reactions, anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and it is most commonly accompanied by severe systemic skin and/or mucosal reactions. The investigator is advised to carefully examine symptoms of adverse reactions observed during or shortly after exposure to Durvalumab and Trametinib, and consider the above mentioned facts prior to making a final diagnosis. Reactions occurring at the time of or shortly after subsequent infusions of investigational product are to be judged by the investigator at his/her own discretion. For the Investigator's convenience and in order to facilitate consistency in judgments a copy of the National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) guidance for anaphylaxis diagnosis is provided in Appendix 2.

7.3.1 **Time Period for Collection of Adverse Events**

Adverse events will be collected from time of signature of informed consent, enrollment, throughout the treatment period and including the follow-up period of
30 days after the last dose of study medication. Serious adverse events will be recorded from the time of informed consent signature through 30 days after the last dose of study medication.

7.3.2 **Follow-up of Unresolved Adverse Events**

Any AEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary. After 90 days, only subjects with investigational product-related SAEs will continue to be followed for safety.

7.4 **Investigator Communications with AstraZeneca/Medimmune**

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period

immediately following the time that written informed consent is obtained through 90 days after the last dose of durvalumab or until the initiation of alternative anticancer therapy. The investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

The investigator will forward all SAE reports to Medimmune/AstraZeneca. A copy of the SAE report must be emailed to Medimmune/AstraZeneca at the time the event is reported.
***** A ***cover page*** should accompany the ***SAE report*** form indicating the following:
"Notification from an Investigator Inititated Study"
The investigator's name and address
The trial name/title and AstraZeneca ISS reference number (ESR-16-12416)

****** MD Anderson must also indicate, either in the SAE report or the cover page, the ***causality*** of events ***in relation to all study medications*** and if the SAE is ***related to disease progression***, as determined by the principal investigator.
**** Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox:*** AEMailboxClinicalTrialTCS@astrazeneca.com

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to Medimmune/AstraZeneca.

Serious adverse events that do not require expedited reporting to the FDA still need to be reported to Medimmine/AstraZeneca using the MD Anderson SAE report form. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

AstraZeneca / MedImmune or designee contact information:

Externally Sponsored Research / Patient Safety
MedImmune
One MedImmune Way
Gaithersburg, MD 20878, USA
Fax: +1-301-398-4205

Investigators should not wait to collect additional information to full document the event before notifying MedImmune Patient Safety of an SAE. When additional information becomes available, investigators should submit a follow-up SAE Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE also needs to be provided to MedImmune Patient Safety within 24 hours of learning of the new information.

Reporting of deaths to AstraZeneca

All deaths that occur during the study or within the protocol-defined 90-day post-last dose of durvalumab safety follow-up period must be reported to AstraZeneca as follows:

Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.

Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to AstraZeneca as a SAE within **24 hours** (see Section 10.3.2 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

Deaths with an unknown cause should always be reported as a SAE.

Deaths that occur following the protocol-defined 90-day post-last-dose of durvalumab safety follow-up period will be documented as events for survival analysis, but will not be reported as an SAE. However, if an investigator learns of any SAEs, including death, at any time after the subject has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify the study AstraZeneca/MedImmune Drug Safety.

Reporting to Novartis

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided the main informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department - Fax: (877-778-9739). The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Warnings and precautions

Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed

7.5 Definitions and **Other Events Requiring Immediate Reporting**

7.5.1 **Overdose**

An overdose is defined as a subject receiving a dose of investigational product in excess of

that specified in the Investigator's Brochure, unless otherwise specified in this protocol. Any overdose of a study subject with the investigational product, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 7.5 for contact information). If the overdose results in an AE, the AE must also be recorded on the AE eCRF. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE (see Section 7.4 and Section 7.5). MedImmune does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

7.5.2 **Hepatic Function Abnormality**

Adverse events of hepatic function abnormality of special interest to the MedImmune (AstraZeneca) and Novartis are defined as any increase in ALT or AST to greater than 3 × ULN **and concurrent** increase in bilirubin to greater than 2 × ULN (ie, Hy's law cases). Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. In the event of hepatic function abnormality where the etiology is unknown, timely follow-up investigations and inquiries should be initiated by the investigational site, based on medical judgment, to make an informed decision regarding the etiology of the event.

If the underlying diagnosis for the hepatic function abnormality is known (including progression of pre-existing disease such as primary or metastatic malignancy), the diagnosis should be recorded as an AE/SAE. If the underlying diagnosis for the hepatic function abnormality remains unknown, the term "hepatic function abnormal" should be used to report the AE/SAE. Hepatic function abnormality of unknown etiology, or which is considered attributable to investigational product, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the SAE Report Form, even if the event is considered to be non-serious (see Section 7.5 for contact information). The investigator will review the data with the AstraZeneca / MedImmune . The investigator should then use clinical judgment to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated.

If, after appropriate workup, in the opinion of the investigator, the underlying diagnosis for the abnormality remains unexplained, or is considered attributable to investigational product, permanent discontinuation of dosing for the study subject should be considered. Each reported event of hepatic function abnormality will be followed by the investigator. If the etiology of the event remains unconfirmed and/or is considered related to investigational product, a prompt cumulative review of safety data and the circumstances of the event in question will be conducted and assessed by the AstraZeneca / MedImmune safety review committee (or equivalent) to determine whether continued dosing of current

study subjects and/or study entry should be interrupted, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the MedImmune safety review committee (or equivalent) is required for resumption of subject dosing or study entry in the event that the study is interrupted. Where applicable, regulatory authorities IRBs/IECs will be notified of any actions taken with the study.

7.5.3 **Pregnancy**

Pregnancy in a female subject who has received investigational product is required to be reported ***within 24 hours of knowledge of the event*** to AstraZeneca / MedImmune Patient Safety using the MD Anderson SAE form (see Section 7.5 for contact information). Subjects who become pregnant during the study period must not receive additional doses of investigational product but will not be withdrawn from the study. The pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to MedImmune Patient Safety after outcome. Should the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product this should be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 7.5 for contact information). The investigator will endeavor to collect follow-up information on such pregnancies provided the partner of the study subject provides consent.

Maternal exposure

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate AstraZeneca representatives within 1 day, ie, immediately, but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies. The same timelines apply when outcome information is available.

Paternal exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab + any drug combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose of durvalumab + any drug combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

7.5.4 **Pneumonitis**
Adverse events of pneumonitis are required to be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the MD Anderson SAE form (see Section 7.5 for contact information).

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study is presented in Section 7.1.

8.1 **Identity of Investigational Products**
MedImmune and Novartis will provide the investigators with investigational product using designated distribution centers (Table 8.1).

Table 8.1 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
Durvalumab	MedImmune	Supplied as a vialed liquid solution containing 500 mg (nominal) Durvalumab per vial. The solution contains 50 mg/mL Durvalumab, 26 mM histidine/histidine HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, at pH 6.0
Trametinib	Novartis	Trametinib tablets are supplied as 0.5-mg, 1-mg, and 2-mg tablets for oral administration. Each 0.5-mg tablet contains 0.5635 mg trametinib dimethyl sulfoxide equivalent to 0.5 mg of trametinib non-solvated parent.

		Each 1-mg tablet contains 1.127 mg trametinib dimethyl sulfoxide equivalent to 1 mg of trametinib non-solvated parent. Each 2-mg tablet contains 2.254 mg trametinib dimethyl sulfoxide equivalent to 2 mg of trametinib non-solvated parent

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Commercially available IV bags with 0.9% (weight per volume [w/v]) saline or 5% (w/v) dextrose will be supplied by each site. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused Durvalumab will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune according to the investigational site policy. Both investigational products should be kept in a secure and dry place. Durvalumab vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. All unused Trametinib will be disposed of according to investigational site policy.

8.1.1 **Dose Calculation**

The dose of Durvalumab will be fixed 1500mg IV q4 weeks. The dose of Trametinib will be between 1-2mg PO daily.

Durvalumab

Durvalumab will be given intravenously at a dose of 1500mg every 4 weeks.

Trametinib

Trametinib will be taken orally at a dose between 1-2mg. Patients will self-administer at home

8.1.2 **Investigational Product Inspection**

Durvalumab

Durvalumab will be supplied as a 500 mg/vial concentrate for solution for infusion. The solution contains 50 mg/mL Durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% (w/v) polysorbate 80; it has a pH of 6.0. If there are any defects noted with the investigational product, the investigator should be notified immediately. Refer to the Product Complaint section for further instructions.

Durvalumab will be supplied to the site in vials in coded kits. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each vial within the carton). Each vial selected for dose preparation should be inspected. If there are any defects noted with the investigational product(s), the investigator should be notified immediately. Refer to the Product Complaint section (Section 8.1.6) for further instructions.

Trametinib

The drug substance is blended with inert ingredients (mannitol, sodium lauryl sulfate, colloidal silicon dioxide, microcrystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate) and compressed into tablets. The tablets are then coated with a white or pink opaque film (Opadry White or Pink, a titanium dioxide-based formulation with iron oxide as colorant, as applicable).

Trametinib will be dosage in tablets with unit dose strengths of 0.5 mg. The route of administration will be oral, continuous through the study, unless toxicity is presented, once daily. Trametinib should be administered under fasting conditions, either one hour before or 2 hours after a meal. Trametinib should be administered with approximately eight ounces of water. If a subject vomits after taking study medication, the subject should be instructed not to retake the dose and should take the next scheduled dose.

If a subject misses a dose, subject may take the dose if the next scheduled dose is at least 12 hours later. If the next scheduled dose is due in less than 12 hours, subject should skip the dose and resume dosing the next day at the regular time.

Trametinib tablets are packaged into a high density polyethylene (HDPE) bottle that contains desiccant with a child-resistant closure that includes an induction seal liner. The HDPE bottle is enclosed in a paperboard carton.

8.1.3 **Dose Preparation Steps**

Durvalumab
Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

A dose of 1500mg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 30.0 mL of durvalumab (MEDI4736) (ie, 1500mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion into a peripheral or central vein. Following preparation of durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes). Less than 55 minutes is considered a deviation, the total allowed time should not exceed 8 hours at room temperature.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

8.1.4 **Treatment Administration**

The first day of durvalumab dosing is considered Day 1.

Durvalumab should be administered using the following guidelines:

1. Investigational product must be administered at room temperature by controlled infusion into a peripheral vein or central line. Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.

2. A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product(s). Fully functional resuscitation facilities should be available. Investigational product(s) must not be administered via IV push or bolus but as an IV infusion. The entire content of each IV bag will be infused using an infusion pump.

3. The infusion lines should be attached only at time of use. Lines used for infusion during dose administration will need to be equipped with 0.22- or 0.2-µm in-line filters. Durvalumab solution should not be infused with other solutions or medications.

4. The entire contents of the IV bag should be administered as an IV infusion for approximately 1 hour. Some investigational product may remain in the IV line after the infusion has completed. Fifteen to 30 mL of IV solution should be added to the infusion bag after the investigational product has been administered to flush the line. The infusion rate

should not be changed unless necessary to manage acute reactions. Document if the line was not flushed.

8.1.5 **Monitoring of Dose Administration**

Subjects will be monitored prior to, during, and after infusion of Durvalumab. Vital signs (temperature, BP, pulse rate, and respiratory rate) will be measured on treatment days within 30 minutes prior to the start of Durvalumab administration, every 30 minutes (± 5 minutes) during Durvalumab administration, at the end of Durvalumab infusion (+ 5 minutes), and at 30 and 60 minutes (± 5 minutes) post end of infusion of Durvalumab. For Dose 1, an additional 2-hour (± 15 minutes) observation period will be required after the 60 minutes (± 5 minutes) post end of infusion of Durvalumab vital sign assessment. The additional 2-hour observation period will not be required for subsequent doses unless the subject experiences an infusion reaction.

In the event of Grade ≤ 2 infusion-related reaction, the infusion rate of Durvalumab may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. In subjects experiencing Grade ≤ 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate.

Primary prophylaxis against infusion-related reactions is not permitted during this study in order to avoid obscuring a potential safety signal and enable a future assessment regarding whether premedications should be required for all subjects in future studies. However, at the discretion of the investigator, secondary prophylaxis (ie, prevention of infusion-related reaction following initial episode) is appropriate and will be permitted. Acetaminophen and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade 3 or higher in severity, treatment with Durvalumab will be discontinued.

As with any mAb, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

8.1.6 **Reporting Product Complaints**

Any defects with Durvalumab must be reported immediately to MedImmune. Any defects with Trametinib must be reported immediately to Novartis.

8.1.7 **Additional Study Medications**

No other study medications are specified for use in this clinical protocol.

8.1.8 **Labeling**

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. Label text will be translated into local languages, as required.

8.1.9 **Storage**

Store Durvalumab at 2°C to 8°C (36°F to 46°F). Do not freeze.

Store Trametinib refrigerated at 2° to 8°C (36° to 46°F). Do not freeze. Dispense in original bottle. Do not remove desiccant. Protect from moisture and light. Do not place medication in pill boxes.

8.1.10 **Treatment Compliance**
Investigational product is administered by study site personnel, who will monitor compliance.

8.1.11 **Accountability**

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned along with all unused investigational product.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Laboratory Correlative Studies

All correlative studies will be performed by the Immune Platform at MD. Samples include tumor biopsy samples prior to checkpoint inhibitor therapy and at the start of cycles 2 and 4. Biopsies are optional, though at MTD paried biopsies are mandatory in 15 patients. Peripheral blood samples will be collected in tubes at the time points outlined in section 5 and in the study calendar in section 10. The exact collection methodology and standard operative procedures will be listed in a laboratory manual. We will be attempting to uncover biomarkers associated with safety and relapse-free survival by quantifying:

1. Pre- and post-immune checkpoint inhibitor therapy effect on T-effector cell populations; CD4 subsets; T-regulatory populations; B cell populations; dendritic and macrophage populations.
2. Pre- and post-immune checkpoint inhibitor therapy on functional assays related to Teff cells.

3. Analysis of PD-L1 expression in tumor cells and infiltrating immune cells pre- and post-treatment.
4. Immunologic markers obtained in peripheral blood versus those obtained at the tissue level.
5. Immunologic biomarkers obtained in the tissue and peripheral blood correlated with safety, feasibility, and progression free survival.

These will be reported via:

1. Graphical displays will be used to display all biomarker data a baseline and follow-up. Transformation will be used as needed prior to hypothesis testing and estimating summary statistics. We will use a paired t test to determine if there is a difference in pre- and post-immune checkpoint inhibitor therapy in T-effector cell populations; T-regulatory populations; CD4 subsets; B cell populations; dendritic and macrophage populations.
2. We will use scatterplots to demonstrate correlation between immunologic markers obtained in peripheral blood versus those obtained at the tissue level. A Pearson correlation will be estimated to describe the level of association.

10. STUDY CALENDAR

	Wk -1 +/-3d	Wk 0 +/-3d	Wk 2 +/-3d	Wk 4 +/-3d	Wk 6 +/-3d	Wk 8	Wk 12 (every 4 wks)	Wk 16 (every 8 wk)	Comment
Durvalumab		X		X		X	X		
Trametinib	X	X	X	X	X	X	X		
Clinic Visit	X	X	X	X	X	X	X		
Targeted Physical Examination	X	X	X	X	X	X	X		Targeted examination must include HEENT, CHEST, CV, ABD, SKIN, and NEURO
Vital Signs and Oxygen Saturation	X	X	X	X	X	X	X		Including BP, HR, temperature and oxygen saturation by pulse oximetry (at rest). Obtain vital signs within 72 hours prior to first dose.
Physical Measurements (including performance status)	X	X	X	X	X	X	X		Weight and ECOG performance status. See Appendix 1 for ECOG Performance Status scale.
Review of Concomitant Medication	X	X	X	X	X	X	X		
Laboratory Tests	X	X	X	X	X	X	X		On-study local laboratory assessments should be done within 72 hours prior to each dose: CBC w/differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), comprehensive metabolic panel, Mg)*
Pregnancy test (WOCBP only)	X								Serum or urine pregnancy test to be done within 24 hours prior to first dose.
ECOG PS	X	X		X		X	X		
Adverse Events Assessment	X	X	X	X	X	X	X		Per CTCAE v4.03
End of treatment visit									Approximately 28 days (+/-7days after last treatment, Preferred in clinic visit though maybe via phone call**
CT C/A/P with IV contrast with tumor measurements						X		X	
Biopsy (tumor) optional (mandatory for 15 at MTD)	X			X					
Immunogenicity Assessments, Peripheral Blood	• Week -1, week0, week 4, week 8, week 12, and progression, up to 8 tubes of blood with 10ml each will be collected for immunological assessment. See section 5.1.3 (up to 2 missed blood draws are allowed)								

- Comprehensive metabolic panel: BUN or serum urea level, creatinine, Ca, Na, K, Cl, glucose, and bicarbonate
- *CEA, TSH and FT4 at week 4 and 8 and then every 8weeks
- *amylase and lipase with week 8

** Subjects who decline to return to the site for evaluations will be offered follow-up by **phone every 3 months** as an alternative

11. MEASUREMENT OF EFFECT

Immune related response criteria (irRC) described by Wolchok et al. will be used to identify measurable disease on baseline CT scans. Further imaging will be performed according to the study outline in section 5 and study calendar in section 10.

11.1.1. **Definitions**

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of enrollment.

Evaluable for response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

11.1.2 **Disease Parameters**

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (<10 mm using CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

11.1.3 **Methods for Evaluation of Measurable Disease**

Response and progression will be evaluated in this study using guidelines proposed by the Immune Related Response Criteria (irRC).

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 2 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

11.1.3.1 irRC: Measurable Disease

Index lesions: Must be accurately measured in two dimensions, with a minimum size of ≥5 x 5mm (two largest perpendicular diameters) by CT scan (CT scan slice thickness no greater than 5 mm) or 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

11.1.3.2 irRC: Index and non-Index Lesions:

For the irRC, only index and measurable new lesions are taken into account (in contrast to conventional WHO criteria, which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden). At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5 x 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden.

11.1.4 **Response Criteria**

11.1.4.1 *Immune Related Response Criteria (irRC)*

Evaluation of Target Lesions

Response in new patients will be conducted using the Immune Related Response Criteria (irRC), as described by Wolchok, et al 60. "For irRC, only index and measurable new lesions are taken into account. At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5 x 5mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden:"

Tumor Burden=SPDindex lesions + SPDnew, measurable lesions

Complete Response (irCR): irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented.

Partial Response (irPR): irPR, decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment at least 4 wk after first documentation.

Progressive Disease (irPD): irPD, increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented.

If a patient is classified as having irPD at a post-baseline tumor assessment, then confirmation of irPD by a second scan in the absence of rapid clinical deterioration is required. The definition of confirmation of progression represents an increase in tumor burden ≥25% compared with the nadir at two consecutive time points at least

4 wk apart. It is recommended that this be done at the discretion of the investigator because follow-up with observation alone may not be appropriate for patients with a rapid decline in performance status.

Stable Disease (irSD): irSD, not meeting criteria for irCR or irPR, in absence of irPD.

Table 2. Derivation of irRC overall responses

Measurable response	Nonmeasurable response		Overall response
Index and new, measurable lesions (tumor burden),* %	Non-index lesions	New, nonmeasurable lesions	Using irRC
↓100	Absent	Absent	irCR†
↓100	Stable	Any	irPR†
↓100	Unequivocal progression	Any	irPR†
↓≥50	Absent/Stable	Any	irPR†
↓≥50	Unequivocal progression	Any	irPR†
↓<50 to <25↑	Absent/Stable	Any	irSD
↓<50 to <25↑	Unequivocal progression	Any	irSD
≥25?	Any	Any	irPD†

*Decreases assessed relative to baseline, including measurable lesions only (>5 × 5 mm).
†Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 wk apart.

Table 1. Comparison between WHO criteria and the irRC

	WHO	irRC
New, measurable lesions (i.e., ≥5 × 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 × 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

12. DATA REPORTING REQUIREMENTS / STUDY AND DATA MANAGEMENT

12.1 Monitoring of the Study

During the study, a MedImmune representative will be available if the investigator(s) or other staff at the center needs information and advice about the study conduct.

12.2.1 **Source Data**

Data source will be at MD Anderson Cancer Center.

12.2.2 **Study Agreements**

The principal investigator should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

12.2.3 **Archiving of Study Documents**

The investigator follows the principles outlined in the Clinical Study Agreement.

12.3 Study Timetable and End of Study

The end of the study ("study completion") is 1.5 years after the final subject is enrolled or the date the study is closed by MedImmune (AstraZeneca) and Novartis, whichever occurs first.

12.4 Data Management

The investigator ensures the accuracy, completeness, and timeliness of the data recorded.

13. STATISTICAL CONSIDERATIONS

This is a phase II open-label study to assess the efficacy and safety of the combination therapy with Durvalumab and Trametinib in MSS metastatic colon cancer patients. The primary endpoint is the best overall response (CR+PR) by immune response criteria. Up to 44 patients will be enrolled and treated at the MTD of the combination therapy. We conservatively expect to enroll between 4-6 patients per month on this protocol, requiring a total of approximately 10-12 months to complete enrollment. The Simon's two-stage minimax design will be implemented based on a null hypothesis of 5% response rate and an alternative hypothesis of 15% response rate. In the first stage, we will enroll 29 patients; if 1 or fewer achieves response, patient enrollment will be stopped. Otherwise, we will continue to enroll all 44 patients and the combination therapy is deemed as promising if there are 5 or more responders. For efficacy monitoring purposes if inadequate responses are seen to proceed to the second stage, then the final assessment for response will occur 6months following the enrollment of the last patient. The design has a one-sided type I error rate of 0.10 and 80% power. The probability of early termination is 57% under the null hypothesis. Patient enrollment will be temporarily suspended when the enrollment for the first stage is completed yet not enough responders have been observed to trigger the start of the second stage.

Additionally, toxicities (defined as any treatment related Grade 3 or higher toxicities) will be monitored using the Bayesian method of Thall, Simon and Estey. The toxicity

stopping rule to be applied is to stopped the trial early if Prob(p>0.35 |data) > .92, where p denotes the probability of toxicity. This decision criterion will be applied after the first 8 patients have been evaluated, and then in cohort size of 6. Assuming a beta (1,1) priori for p, the stopping boundaries corresponding are shown in Table 1 below. For example, we will stop the trial if 8 or more patients experienced treatment related Grade 3 or higher toxicities among the first 14 evaluable patients.

Toxicity monitoring will occur during the first cycle of therapy.

The Investigator is responsible for completing efficacy/toxicity summary reports.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

Table 1. Toxicity stopping boundaries

Number of evaluable patients	Number of patients with toxicities is **at least**
8	5
14	8
20	10
26	13
32	15
38	18
44	20

The operating characteristics of this study design based on 10,000 simulations are illustrated in Table 2.

Table 2. Operating Characteristics for Toxicity Monitoring Rule.

True toxicity rate	Prob (stop early)	Median (25^{th}, 75^{th} percentile)
0.10	0.001	44 (44, 44)
0.20	0.016	44 (44, 44)
0.30	0.114	44 (44, 44)
0.35	0.237	44 (44, 44)
0.40	0.410	44 (20, 44)
0.50	0.824	20 (8, 32)
0.60	0.981	8 (8, 14)

Statistical software used Multc Lean Desktop V2.1.

The best response (CR/PR) rate will be estimated along with the exact 95% confidence interval. Patients who drop out of the study prior to the assessment of response will be counted as non-responders for the primary analysis. Safety data will be summarized using descriptive statistics. Time-to-event outcomes, including time to treatment failure (i.e., death, progression or treatment related toxicities are counted as events), or progression-free survival (i.e., death or progression are counted as events) will be estimated using the Kaplan-Meier method.

The immunological and molecular biomarker changes (such as CD4 and CD8 T-cell) will be summarized over time using descriptive statistics and graphical display. A paired t-test will be used to determine if there is a statistically significant change between pre- and post-treatment. The correlation between change in CD8+ T-cell density from pre-treatment to on-treatment biopsy tumor tissue will be conducted based on Pearson's correlation coefficient and Spearman's rank correlation coefficient. With 15 paired biopsy samples, assuming normally distributed data and two-sided 0.05% alpha, we will have 80% power to detect a 0.723*s (where "s" is the within group standard deviation) or greater effect size, represented by change in immune cell markers with treatment.

REFERENCES

1. Siegel, R., et al., Cancer statistics, 2014. CA Cancer J Clin, 2014. 64(1): p. 9-29.
2. Scheele, J., et al., Resection of colorectal liver metastases. World J Surg, 1995. 19(1): p. 59-71.
3. Adam, R. and E. Vinet, Regional treatment of metastasis: surgery of colorectal liver metastases. Ann Oncol, 2004. 15 Suppl 4: p. iv103-6.
4. Parkin, D.M., et al., Global cancer statistics, 2002. CA Cancer J Clin, 2005. 55(2): p. 74-108.
5. Gustavsson, B., et al., A Review of the Evolution of Systemic Chemotherapy in the Management of Colorectal Cancer. Clin Colorectal Cancer, 2015. 14(1): p. 1-10.
6. Svensson, H., et al., Accumulation of CCR4(+)CTLA-4 FOXP3(+)CD25(hi) regulatory T cells in colon adenocarcinomas correlate to reduced activation of conventional T cells. PLoS One, 2012. 7(2): p. e30695.
7. Katz, S.C., et al., Regulatory T cell infiltration predicts outcome following resection of colorectal cancer liver metastases. Ann Surg Oncol, 2013. 20(3): p. 946-55.
8. Lawrence, M.S., et al., Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature, 2013. 499(7457): p. 214-8.
9. Rooney, M.S., et al., Molecular and genetic properties of tumors associated with local immune cytolytic activity. Cell, 2015. 160(1-2): p. 48-61.
10. Maio, M., et al., Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. J Clin Oncol, 2015. 33(10): p. 1191-6.
11. Schadendorf, D., et al., Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol, 2015. 33(17): p. 1889-94.
12. Robert, C., et al., Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med, 2015. 372(26): p. 2521-32.
13. Larkin, J., et al., Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med, 2015. 373(1): p. 23-34.
14. Hanahan, D. and R.A. Weinberg, Hallmarks of cancer: the next generation. Cell, 2011. 144(5): p. 646-74.
15. Shields, J.D., et al., Induction of lymphoidlike stroma and immune escape by tumors that express the chemokine CCL21. Science, 2010. 328(5979): p. 749-52.
16. Monti, S., et al., Molecular profiling of diffuse large B-cell lymphoma identifies robust subtypes including one characterized by host inflammatory response. Blood, 2005. 105(5): p. 1851-61.
17. Gooden, M.J., et al., The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis. Br J Cancer, 2011. 105(1): p. 93-103.
18. Baitsch, L., et al., The three main stumbling blocks for anticancer T cells. Trends Immunol, 2012. 33(7): p. 364-72.
19. Crespo, J., et al., T cell anergy, exhaustion, senescence, and stemness in the tumor microenvironment. Curr Opin Immunol, 2013. 25(2): p. 214-21.

20. Wolchok, J.D., et al., Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res, 2009. 15(23): p. 7412-20.
21. Hodi, F.S., et al., Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med, 2010. 363(8): p. 711-23.
22. Robert, C., et al., Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med, 2011. 364(26): p. 2517-26.
23. Brahmer, J.R., et al., Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol, 2010. 28(19): p. 3167-75.
24. Topalian, S.L., et al., Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer. New England Journal of Medicine, 2012. 366(26): p. 2443-2454.
25. Brahmer, J.R., et al., Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer. New England Journal of Medicine, 2012. 366(26): p. 2455-2465.
26. Harzstark, A.L. and E.J. Small, Castrate-resistant prostate cancer: therapeutic strategies. Expert Opin Pharmacother, 2010. 11(6): p. 937-45.
27. Slovin, S.F., et al., Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multicenter phase I/II study. Ann Oncol, 2013. 24(7): p. 1813-21.
28. Royal, R.E., et al., Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother, 2010. 33(8): p. 828-33.
29. Calabro, L., et al., Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial. Lancet Oncol, 2013. 14(11): p. 1104-11.
30. Oganesyan, V., et al., Structural characterization of a human Fc fragment engineered for lack of effector functions. Acta Crystallogr D Biol Crystallogr, 2008. 64(Pt 6): p. 700-4.
31. Hamanishi, J., et al., Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc Natl Acad Sci U S A, 2007. 104(9): p. 3360-5.
32. Wang E, Kang D, et al. Population pharmacokinetic and pharmacodynamics analysis of tremelimumab in patients with metastatic melanoma. J Clin Pharmacol. 2014 Oct; 54(10):1108-16.
33. Ng CM, Lum BL, Gimenez V, et al. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res. 2006;23(6):1275–84.
34. Wang DD, Zhang S, Zhao H, et al. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009;49(9):1012–24.
35. Zhang S, Shi R, Li C, et al. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol. 2012;52(1):18–28.
36. Narwal R, Roskos LK, Robbie GJ (2013) Population Pharmacokinetics of Sifalimumab, an Investigational Anti-Interferonalpha Monoclonal Antibody, in Systemic Lupus Erythematosus. Clin Pharmacokinet 52:1017–1027

2017-0514
December 19, 2017
Page 126

2017-0514
December 19, 2017
Page 127

APPENDIX 1

Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

2017-0514
December 19, 2017
Page 128

2017-0514
December 19, 2017
Page 129

Appendix 2
National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network guidance for Anaphylaxis Diagnosis

The NIAID and FAAN define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death [64]. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips, tongue, uvula)
AND AT LEAST ONE OF THE FOLLOWING:
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

[1] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD
[2] NCI CTCAE version 4.03
[3] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD
[4] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation