# NSABP PROTOCOL FC-9

# A Phase II Study of the Dual Immune Checkpoint Blockade with Durvalumab (MEDI4736) plus Tremelimumab Following Palliative Hypofractionated Radiation in Patients with Microsatellite Stable (MSS) Metastatic Colorectal Cancer Progressing on Chemotherapy


**NSABP Foundation, Inc.**

[redacted]

**TELEPHONE:** [redacted]
**E-MAIL:**
**CLINICAL QUESTIONS:**


**KEY STUDY PERSONNEL**

| | |
|---|---|
| NSABP Chair: | Norman Wolmark, MD |
| NSABP Medical Director: | Samuel Jacobs, MD |
| Protocol Chair: | James J. Lee, MD, PhD |
| Protocol Officer: | Thomas George, MD |
| Protocol Statistician: | Greg Yothers, PhD |
| Radiation Therapy Co-Chair: | Dwight Heron, MD |


**Protocol FC-9 IND #132833 (Durvalumab), (Tremelimumab)**
**sponsored by the NSABP Foundation, Inc.**

Version Date: April 17, 2019 (Replaces all other versions)


**CONFIDENTIAL**

# PROTOCOL REVISION RECORD

**Original Version:** October 17, 2016

**Amendment #1:** November 22, 2016

**Amendment #2:** January 25, 2017

**Amendment #3:** March 28, 2017

**Amendment #4:** June 26, 2017

*NSABP FC-9 Protocol and consent amended prior to activation of the study.*

***Amendment #5:*** May 8, 2018

Title page

Protocol Revision Record

| | |
|---|---|
| Section 4.0 | 4.2,10, 4.2.20 |
| Section 8.0: | 8.4 (Table 7), 8.5, 8.5.1, 8.5.2, 8.5.3, 8.5.4, 8.5.5, 8.5.6, 8.5.7, 8.5.8, 8.5.9, 8.5.10, 8.5.11, 8.5.12, 8.5.13 (added) |
| Section 9.0 | 9.5 |
| Section 10.0 | 10.2 |
| Section 16.0 | Reference updated |

*The NSABP FC-9 consent has been amended.*

***Amendment #6:*** November 15, 2018

Title page

Protocol Revision Record

| | |
|---|---|
| Section 1.0 | Overview, Schema |
| Section 5.0 | Table 2 |
| Section 7.0 | 7.1 (Table 4) |
| Section 9.0 | 9.1.4, 9.2.4 |
| Section 14.0 | 14.1 |

***Amendment #7*** April 17, 2019

Title page

Protocol Revision Record

| | |
|---|---|
| Section 10.0 | 10.2 |

Appendix C

**TABLE OF CONTENTS**

## INFORMATION RESOURCES

| | | |
|---|---|---|
| **NSABP Department of Site and Study Management**<br>NSABP Operations Center<br>[redacted]<br>Phone: [redacted] E-mail: [redacted] | | |
| **For questions regarding:**<br>• IRB review & informed consent<br>• Submission of IRB approval<br>• Study entry information<br>• Eligibility<br>• Treatment regimen<br>• Dose modifications/delays<br>• Other clinical aspects of the trial<br>• Adverse event reporting including SAE reporting<br>• eCRF completion | Department of Site and Study Management (DSSM) | Phone: [redacted]<br>E-mail: [redacted] |
| **For questions regarding data management** | Department of Site and Study Management (DSSM) | Phone: [redacted]<br>E-mail: [redacted] |
| **Request for blood sample collection kits** | NSABP Division of Pathology<br>[redacted] | Phone: [redacted]<br>Email: [redacted]<br>Refer to the FC-9 Pathology and Correlative Science Instructions |
| **Requests for durvalumab and tremelimumab** | Department of Site and Study Management (DSSM) | E-mail: [redacted] |
| **Questions regarding drug shipment** | Department of Site and Study Management (DSSM) | Phone: [redacted]<br>E-mail: [redacted] |

## GLOSSARY OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| 5-FU | 5-fluorouracil |
| AChE | acetylcholine esterase |
| ADA | antidrug antibody |
| ADCC | antibody dependent cell-mediated cytotoxicity |
| AE | adverse event |
| Alk phos | alkaline phosphatase |
| ALT (SGPT) | alanine aminotransferase |
| AML | acute myelogenous leukemia |
| ANC | absolute neutrophil count |
| ASCO | American Society of Clinical Oncology |
| AST (SGOT) | aspartate aminotransferase |
| ATP | adenosine triphosphate |
| BNP | Brain natriuretic peptide |
| BRAF | v-raf murine sarcoma viral oncogene homolog B1 |
| BRAFi | BRAF inhibitor |
| BSC | best supportive care |
| BUN | blood, urea, nitrogen |
| CBC | complete blood count |
| CBCT | cone-beam CT |
| CDC | complement-dependent cytotoxicity |
| cDNA | circulating DNA |
| CEA | carcinoembryonic antigen |
| ChemoRT | chemo-radiotherapy |
| CI | confidence interval |
| CPT-11 | irinotecan |
| CR | complete response |
| CRC | colorectal cancer |
| CRT | calreticulin |
| CT | computed tomography |
| CTEP | Cancer Therapy Evaluation Program |
| CTCAE v4.0 | Common Terminology Criteria for Adverse Events Version 4.0 |
| CTLA-4 | cytotoxic T-lymphocyte-associated protein 4 |
| D/C | discontinue |
| DAMP | damage-associated molecular patterns |
| DC | dendritic cell |
| DCO | data cutoff |
| dL | deciliter |
| DNA | deoxyribonucleic acid |
| DSSM | Department of Site and Study Management |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EGRF | epidermal growth factor receptor |

## GLOSSARY OF ABBREVIATIONS AND ACRONYMS (Continued)

| | |
|---|---|
| Fcγ | fragment crystallizable gamma |
| FACS | fluorescence-activated cell sorting |
| FDA | Food and Drug Administration |
| FDG-PET | Fluorine-18-fluorodeoxyglucose Positron Emission Tomography |
| FFPE | formalin-fixed paraffin embedded |
| G-CSF | granulocyte-colony stimulating factor |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| GITR | glucocorticoid-induced tumor necrosis factor receptor related protein |
| GLP | Good Laboratory Practice |
| GTV | gross tumor volume |
| GY | gray |
| H&P | history and physical |
| HCC | hepatocellular carcinoma |
| HMGB1 | high-mobility group box 1 protein |
| HR | hazard ratio |
| IB | Investigators Brochure |
| ID | identification |
| IDO | indoleamine 2, 3-Dioxygenase |
| IFN-γ | interferon gamma |
| Ig | immunoglobulin |
| IgG1κ | immunoglobulin G1 kappa |
| IGRT | Image-Guided Radiation Therapy |
| IHC | immunohistochemistry |
| ILD | interstitial lung disease |
| IM | intramuscular |
| IND | investigational new drug |
| iNOS | inducible nitric oxide synthase |
| INR | international normalized ratio |
| imAE | immune-related adverse event |
| IRB | institutional review board |
| IU/L | international units per liter |
| IV | intravenous |
| kDa | kilo Dalton |
| kg | kilogram |
| KRAS | V-Ki-ras2Kirsten rat sarcoma viral oncogene homolog |
| LAG-3 | lymphocyte-activation protein 3 |
| LD | longest diameter |
| LDH | lactate dehydrogenase |
| LFT | liver function tests |
| LLN | lower limit of normal |
| MAb | monoclonal antibody |

## GLOSSARY OF ABBREVIATIONS AND ACRONYMS (Continued)

| | |
|---|---|
| mCR | molecular complete remission |
| mCRC | metastatic colorectal cancer |
| MDS | myelodysplastic syndrome |
| MDSC | myeloid-derived suppressor cells |
| mg | milligram |
| MHC-1 | major histocompatibility complex-1 |
| MI | myocardial infarction |
| MLC | multi-leaf collimator |
| mo | month |
| MRI | magnetic resonance imaging |
| ms | millisecond |
| MSI | microsatellite instability |
| MSI-H | microsatellite instability-high |
| MSS | microsatellite stable |
| NaCl | sodium chloride |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NSABP | NSABP Foundation, Inc. |
| NSCLC | non-small cell lung cancer |
| NYHA | New York Heart Association |
| ORR | overall response rate |
| OS | overall survival |
| p-value | calculated probability |
| PBMC | peripheral blood mononuclear cells |
| pCR | pathologic clinical response |
| PD | progressive disease |
| PD-1 | Programmed cell death-1, proficient |
| PD-L1 | programmed death ligand-1 |
| PET | positron emission tomography |
| PFS | progression-free survival |
| PJP | pneumocystis jirovecii pneumonia |
| PK | pharmacokinetics |
| PO | by mouth |
| PR | partial response |
| PT/INR | prothrombin time/international normalized ratio |
| PTV | planning target volume |
| q | every |
| Q2W | every 2 weeks |
| RECIST | Response Evaluation Criteria in Solid Tumors |

## GLOSSARY OF ABBREVIATIONS AND ACRONYMS (Continued)

| | |
|---|---|
| RILD | radiation-induced liver disease |
| RNA | ribonucleic acid |
| RR | response rates |
| RT | radiation therapy |
| SAE | serious adverse event |
| SARRP | small animal radiation research platform |
| SBRT | stereotactic body radiation |
| SCCHN | squamous cell carcinoma of the head and neck |
| SD | stable disease |
| SOC | standard of care |
| T1DM | Type 1 Diabetes Mellitus |
| T-cell | T lymphocyte |
| TB | total bilirubin |
| TCR | T-cell receptor |
| TIA | transient ischemic attacks |
| TIL | tumor-infiltrating lymphocytes |
| TNF | tumor necrosis factor |
| TTR | time to response |
| ULN | upper limit of normal |
| VEGF | vascular endothelial growth factor |
| WNL | within normal limits |
| WOCBP | women of childbearing potential |
| WT | weight |

## 1.0 OVERVIEW OF STUDY DESIGN

The FC-9 study is designed as a phase II, open label, single arm study of the dual immune checkpoint blockade with the combination of durvalumab and tremelimumab following hypofractionated palliative radiation in patients with microsatellite stable (MSS) metastatic colorectal cancer (mCRC) who have progressed on chemotherapy. The primary aim is to determine the anti-tumor efficacy of the dual immune checkpoint blockade with durvalumab plus tremelimumab. The secondary aims are to determine the clinical benefit rate, duration of response, tolerability and correlates of response. Tumor response at unirradiated target lesions will be measured at baseline and every 2 cycles using RECIST 1.1.

Following three doses of hypofractionated palliative radiation (Days −2, −1, and Day 0 prior to Cycle 1), patients will receive the combination of tremelimumab (75 mg IV infusion) and durvalumab (1500 mg IV infusion) on Day 1 for 4 cycles. Beginning with Cycle 5 through Cycle 24, patients will receive durvalumab alone (1500 mg/IV infusion) on Day 1 of each 28 day cycle.

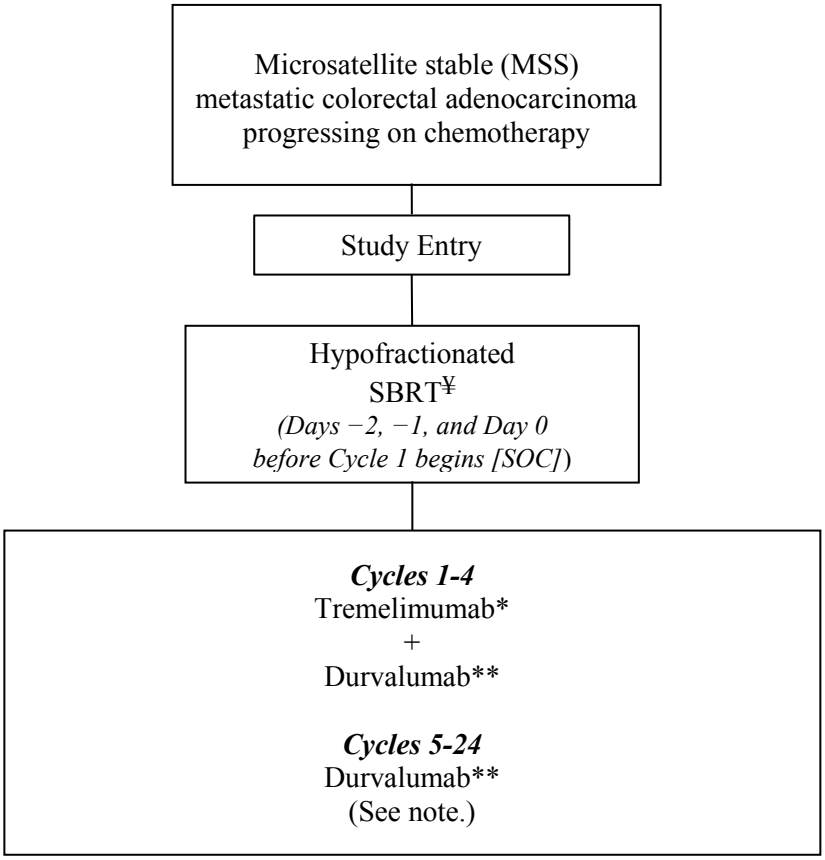
Toxicity will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.0.

The sample size will be between 12 and 21 evaluable patients. Patients who complete both Cycle 1 and Cycle 2, and undergo the first restaging scan after Cycle 2 for the determination of tumor response will be determined evaluable. Non-evaluable patients will be replaced. Twelve evaluable patients will be treated in the first stage of the study. If there are no responses among the 12 evaluable patients, the study will be terminated. If the study goes on to the second stage, a total of 21 evaluable patients will be studied. If the total number responding is less than or equal to 2, the combination will be rejected. If 3 or more responses are observed after the second stage of the study, the combination will be considered for further study.

Submission of tumor tissue and blood samples for FC-9 correlative science studies will be a study requirement for all patients. Requirements will include archived tumor samples from the diagnostic biopsy; additional biopsies of fresh tissue from an accessible lesion prior to radiation therapy and after 2 cycles of study therapy; and blood sample collections.

Figure 1

FC-9 Schema




**¥Hypo-fractionated stereotactic body radiation therapy (SBRT)**

Three doses of palliative hypo-fractionated radiation at 9 Gy/dose will be delivered to a single lesion on ***Days – 2, −1, and Day 0 before Cycle 1 of the study begins***. See Appendix B.

****Tremelimumab cycles 1-4***

- Tremelimumab: 75 mg IV infusion on **Day 1** of Cycle 1 through Cycle 4 (4 doses total).

*****Durvalumab cycles 1-24***

***Note: With Amendment 6, study therapy (as durvalumab alone) is extended from Cycle 5 through Cycle 12 to Cycle 5 through Cycle 24 (approximately 2 years).***

- Durvalumab: 1500 mg IV on **Day 1** of Cycle 1 through Cycle 24 (up to 24 doses total).

*Note:* The duration of each cycle is 28 days.

## 2.0 BACKGROUND

### 2.1 Colorectal Cancer

Colorectal cancer (CRC) is a major public health problem in the U.S. and globally. In the U.S., nearly 50,000 deaths are attributed to this disease on an annual basis (Siegel 2015). When metastatic disease is diagnosed, metastatic CRC (mCRC) is usually associated with poor prognosis, with 5-year survival rates in the 5-8% range. Chemotherapy has been the mainstay approach for patients with metastatic CRC (mCRC). For nearly 40 years, the main drug used was the fluoropyrimidine, 5- fluorouracil (5-FU). Over the past decade, four new cytotoxic anticancer agents have been approved by the U.S. Food and Drug Administration (FDA). These compounds include the topoisomerase I inhibitor irinotecan (CPT-11), the third-generation platinum analog oxaliplatin, the oral fluoropyrimidine capecitabine, and most recently the oral nucleoside TAS-102. Since 2004, six biologic agents have been approved by the FDA, and they include the anti–vascular endothelial growth factor (VEGF) bevacizumab, the anti–epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab, an anti-VEGF recombinant fusion protein aflibercept, a multikinase small molecule inhibitor regorafenib, an anti-VEGFR2 antibody ramucirumab.

Significant advances have been made in chemotherapy treatment options for patients with mCRC with median OS of 24-26 months. Median OS with best supportive care (BSC) alone in patients with mCRC after progression with standard treatment options is historically about 5 months. However, these results continue to fall far short of durable curative treatment of patients with mCRC. There is clearly a significant unmet need for new agents and/or treatment regimens, which may enhance the efficacy of the available anticancer agents, reduce the toxicities of current anticancer agents, and/or improve overall quality of life.

### 2.2 The role of Programmed Death 1 (PD-1) pathway in antitumor immune responses

PD-1 pathway blockade enhances tumor antigen-specific $CD8^+$ T cell responses (Pardoll 2012, Postow 2015). Recently significant advances in the treatment of several tumor types, including melanoma, non-small cell lung cancer, renal cell cancer, bladder cancer, and Hodgkin disease have been made by targeting this specific immunologic signaling pathway. The responses have been highly durable and achieved with minimal toxicity (Brahmer 2012; Patnaik 2012; Topalian 2012; Hamid 2013; Herbst 2014; Ansell 2015).

PD-1 blockade showed a significant antitumor activity in microsatellite instability (MSI)-high colorectal cancer (Le 2015). However, immune checkpoint blockade monotherapy including PD-1 blockade or anti-cytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA-4) therapy has not shown any significant antitumor activity in microsatellite stable (MSS) colorectal cancer (Le 2015; Chung 2010; Brahmer 2010).

### 2.3 Durvalumab

Durvalumab (MEDI4736) is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1), (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274), and CD80 (B7-1) to programmed cell death 1 (PD-1; CD279) (Ibrahim 2015). Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa.

Durvalumab contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

### 2.3.1 *Summary of clinical experience*

As of the data cutoff (DCO) dates, April 15, 2015 to September 18, 2015, (MEDI4736 IB), a total of 1,910 patients have been enrolled and treated in 30 ongoing durvalumab clinical studies, including 20 sponsored and 10 collaborative studies. Of the 1,910 patients, 1,279 received durvalumab monotherapy, 454 received durvalumab in combination with tremelimumab or other anticancer agents, 14 received other agents (1: gefitinib, 13: MEDI6383), and 163 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

### 2.3.2 *Safety*

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Immune-related AEs (imAEs), which are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with durvalumab and tremelimumab combination therapy. The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity. The adverse event profile from two durvalumab monotherapy studies is summarized below:

| ***AEs of any grade in ≥ 5% of patients*** | **CD-ON-1108** 10mg/kg dose N=694 | ***AEs of any grade in ≥ 10% of patients*** | **D4191C00003** 10 mg/kg dose N=303 |
|---|---|---|---|
| Fatigue | 17.7% | Dyspnea | 18.8% |
| Nausea | 8.6% | Fatigue | 12.8% |
| Diarrhea | 7.3% | Decreased appetite | 17.5% |
| Decreased appetite | 6.8% | Cough | 14.2% |
| Pruritus | 6.3% | Pyrexia | 12.2% |
| Rash | 6.1% | Asthenia | 11.9% |
| Vomiting | 5.0% | Nausea | 11.2% |

Treatment-related ≥ Grade 3 events reported in 3 or more patients (≥ 0.4%) in CD-ON-1108 were fatigue (12 patients, 1.7%); increased aspartate aminotransferase (AST; 7 patients, 1.0%); increased gamma-glutamyl transferase (GGT; 6 patients, 0.9%); increased alanine aminotransferase (ALT; 5 patients, 0.7%); and colitis, vomiting, decreased appetite, and hyponatremia (3 patients, 0.4% each). Six patients had treatment-related Grade 4 AEs (upper gastrointestinal hemorrhage, increased AST,

dyspnea, neutropenia, colitis, diarrhea, and pneumonitis) and 1 patient had a treatment-related Grade 5 event (pneumonia).

In study D4191C00003, treatment-related Grade 3 AEs reported in ≥ 2 patients were pneumonitis (3 patients) and increased GGT (2 patients). There were no treatment-related Grade 4 or 5 AEs.

### 2.3.3 *Efficacy*

Efficacy varied by disease and by PD-L1 selection. In PD-L1 unselected patients, the objective response rate (ORR), based on investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, ranged from 0% in uveal melanoma (N = 23) to 20.0% in bladder cancer (N = 15). Across the PD-L1-positive tumors, ORR was highest for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (HCC; N = 3 each, 33.3% each), NSCLC (N = 86, 26.7%), and squamous cell carcinoma of the head and neck (SCCHN; N = 22, 18.2%). Of the 32 patients with myelodysplastic syndrome (MDS) treated in Study D4190C00007, 21 patients had at least 1 post-baseline disease assessment. Among these patients, the best overall responses were molecular complete remission (mCR) in 4 patients (19.0%).

## 2.4 **Tremelimumab**

Tremelimumab is an anti-CTLA-4 IgG2 monoclonal antibody, which blocks the inhibitory signal of CTLA-4/B7 pathway, leading to indirect prolongation and enhancement of T-cell activation and expansion.

Binding of CTLA-4 to its target ligands (B7-1 and B7-2) provides a negative regulatory signal, which limits T-cell activation. Anti-CTLA-4 inhibitors antagonize the binding of CTLA-4 to B7 ligands and enhance human T-cell activation as demonstrated by increased cytokine (interleukin [IL]-2 and interferon gamma [IFN-γ]) production in vitro in whole blood or peripheral blood mononuclear cell cultures (Tarhini 2008). In addition, blockade of CTLA-4 binding to B7 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity (Tremelimumab IB). Therefore, it is expected that treatment with an anti-CTLA-4 antibody, such as tremelimumab, will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

An extensive program of nonclinical and clinical studies has been conducted for tremelimumab both as a monotherapy and as combination therapy with conventional anticancer agents to support various cancer indications using different dose schedules. As of the data cutoff date (November 1, 2015 for monotherapy studies and April 15, 2015 to July 12, 2015 for combination therapy studies), 34 sponsored clinical studies have been conducted as part of the tremelimumab clinical development program. Of these, 13 studies have completed and 21 are ongoing. Eight tremelimumab monotherapy studies have been completed and 3 are ongoing. As of the data cutoff date of November 1, 2015, 973 patients received tremelimumab in completed monotherapy studies and the ongoing Study D4881C00024 and 569 patients have been treated in the ongoing blinded Phase IIb monotherapy Study D4880C00003 [DETERMINE]). In the 3rd ongoing monotherapy study (D4884C00001), no patients have been treated as of the data cutoff. In addition, approximately 59 patients have been treated with tremelimumab in monotherapy arms of combination studies. Five studies of tremelimumab in combination with other anticancer agents have been completed and 18 are ongoing. In total, 250 patients with a variety of tumor types have received tremelimumab in combination with other anticancer agents in these studies.

The profile of adverse events (AEs) and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to patients with melanoma). As of the data cutoff date for monotherapy studies of November 1, 2015, AEs (all grades, regardless of causality) reported in >10% of patients in the completed and rollover tremelimumab monotherapy studies (N=973, integrated data) were diarrhea (45.3%), fatigue (37.5%), nausea (32.5%), rash (28.9%), pruritus (27.4%), decreased appetite (22.8%), vomiting (22.5%), pyrexia (15.3%), cough (15.0%), constipation (14.4%), abdominal pain (13.9%), headache (13.8%), dyspnea (12.4%), and decreased weight (10.3%). Based on integrated data from completed studies of tremelimumab in combination with other agents (N=116), AEs (all grades, regardless of causality) reported in >15% of patients were diarrhea (54.3%); nausea (40.5%); fatigue (38.8%); rash (35.3%); pruritus, decreased appetite (30.2% each); vomiting (27.6%); pyrexia (26.7%); influenza like illness (20.7%); arthralgia (19.8%); constipation (19.0%); thrombocytopenia, injection site reaction (18.1% each); and increased aspartate aminotransferase (AST; 15.5%). Most of these events occurred at a higher rate with tremelimumab plus sunitinib than with other combinations. The events of diarrhea, rash, and pruritus are considered identified risks of tremelimumab. Acute renal failure was reported in patients who received the combination of tremelimumab and sunitinib; however, acute renal failure has not been an expected AE for single-agent tremelimumab. The incidence and/or severity of many of the AEs observed following administration of tremelimumab can be reduced by following current guidelines for the management of immune-related toxicities (Tremelimumab IB).

Chung et al. reported the result of a phase II study of tremelimumab monotherapy in patients with chemo-refractory mCRC (Chung 2010). Patients received tremelimumab 15 mg/kg intravenously (IV) every 90 days until disease progression. Tremelimumab monotherapy did not demonstrate clinically meaningful activity in this patient population (N = 45). However, twenty-one patients (45%) lived >180 days after enrollment, and one patient had partial response (PR). Grade 3/4 treatment-related adverse events (AEs) were diarrhea (N = 5; 11%), ulcerative colitis (N = 1; 2%), fatigue (N = 1; 2%), autoimmune thrombocytopenia (N = 1; 2%), and hypokalemia (N = 1; 2%).

## 2.5 The combination of durvalumab and tremelimumab

Pre-clinical and clinical data suggest that combination of immune checkpoint inhibitors targeting non-overlapping pathways such as durvalumab and tremelimumab may induce synergistic effect leading to improved tumor response in comparison to monotherapy with either agent alone (Pardoll 2012). The combination of agents targeting PD-1/PD-L1 and CTLA-4 has profound and durable clinical benefit in patients with metastatic melanoma (Larkin 2015).

Antonia et al. reported a phase 1, open-label dose escalation and expansion study of durvalumab plus tremelimumab to assess the safety/tolerability and antitumor activity in patients with advanced NSCLC (Antonia 2015). An ORR of 27% was observed in 63 patients. AEs were manageable and generally reversible using standard treatment guidelines. Increasing doses of tremelimumab were generally associated with greater frequency of AEs. Across all dose cohorts, related Grade 3/4 events were reported in 41/102 (40%) patients. Most frequently reported events were colitis, diarrhea, elevated lipase, and elevated liver function tests. 32/102 (31%) patients used corticosteroids. Twenty out of 102 (20%) patients discontinued study therapy due to drug-related AEs. Based on the result of the phase I study of durvalumab/tremelimumab combination, Antonia et al. concluded that the schedule of durvalumab 20 mg/kg every 4 weeks in combination with tremelimumab 1 mg/kg every 4 weeks is appropriate for further development because the schedule: 1) maximizes PD-1/PD-L1 inhibition, which is likely driving overall clinical activity;

2) demonstrates a manageable safety profile; 3) incorporates a biologically active dose of tremelimumab associated with clinical activity (Antonia 2015).

### 2.5.1 *Rationale for fixed dosing of durvalumab and tremelimumab*

A population PK model was developed for durvalumab using monotherapy data from a Phase 1 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 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 approximately 75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrated 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 regimens.

Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (N = 654; doses = 0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma). Population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of ≤ 0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body WT of approximately 75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen (Wang 2014).

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), and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W); is included in the current study.

Fixed dosing of durvalumab and tremelimumab is recommended only for patients with > 30kg body weight due to endotoxin exposure. Patients with a body weight less than or equal to 30 kg should be dosed using a weight-based dosing schedule.

## 2.6 Effect of radiation on immune response to cancer cells

### 2.6.1 *Immunogenic Cell Death by Radiation*

Radiation causes immunogenic cell death of cancer cells, modulates antigen presentation by cancer cells, and alters the microenvironment within the irradiated field (Esposito 2015). The immunogenic cell death of cancer cells involves a multistep process. The release of fractalkine, nucleotides, and adenosine triphosphate (ATP) attract phagocytes or dendritic cells, and the expression of calreticulin (CRT) facilitates recognition by phagocytes or dendritic cells. The release of danger-associated molecular patterns such as high-mobility group box 1 protein (HMGB1) and ATP, which enable dying tumor cells to lose the propensity to induce tolerance and to stimulate powerful anticancer immune responses (Zitvogel 2010; Golden 2012). Immunogenic cell death by

radiotherapy involves the cell surface exposure of CRT, and the release of HMGB1, and ATP that triggers dendritic cell (DC) engulfment of dying cells, antigen presentation, and production of interleukin (IL)-1β, ultimately leading to activation of $CD8^+$ T cells (Esposito 2015).

Low-dose radiation programs the differentiation of $iNOS^+$ M1 macrophages that orchestrate CTL recruitment into and killing within solid tumors through iNOS by inducing endothelial activation and the expression of Th1 chemokines and by suppressing the production of angiogenic, immunosuppressive, and tumor growth factors. $iNOS^+$ macrophages in the tumor microenvironment are both required and sufficient to mediate effector T cell recruitment into tumor tissue and successful tumor immune rejection through an NO-dependent mechanism (Klug 2013).

### 2.6.2 *Abscopal effect of radiation*

The abscopal effect is a phenomenon in which local radiotherapy is associated with the regression of other metastatic lesions distant from the irradiated site. Postow et al. (Postow 2012) reported a case of the abscopal effect in a patient with melanoma treated with ipilimumab and palliative radiation. Localized radiation therapy was administered to the metastasis for pain control. The target tumor decreased and, in addition, the distant metastatic disease in lymph nodes and spleen also regressed. The off-target regression in progressive metastatic disease after local irradiation with immunotherapy was correlated with activation of a T-cell population suggesting that radiation may have played an immunomodulatory role (Postow 2012). Thus, this "abscopal effect" (immunomodulatory effects on systemic cancer burden with local radiotherapy) appears related to a host of effects related to local radiation-induced release of damage-associated molecular patterns (DAMP), such as cancer-associated neoantigens, secretion of pro-inflammatory cytokines without concurrent systemic immunosuppressive effects, upregulation of immunogenic cell surface markers on cancer and surrounding stroma, increased homing of immune cells to tumors and improved antigen presentation by antigen-presenting cells (Formenti 2009, Formenti 2012 Formenti 2013; Gaipl 2014).

Anecdotal reports describe durable abscopal effects in patients who received palliative doses of radiation during treatment with immunomodulatory therapies such as anti-CTLA-4 or PD-1/PD-L1 pathway blockade (Sagiv-Barfi 2014, Postow 2012).

## 2.7 The combination of radiation and immune checkpoint inhibitors

### 2.7.1 *Radiation plus ipilimumab promotes regression of unirradiated tumors in patients with melanoma*

Twyman-Saint Victor et al. reported major tumor regressions in a subset of patients with metastatic melanoma treated with an anti-CTLA4 antibody (ipilimumab) and radiation (Twyman-Saint Victor 2015). To examine the feasibility and efficacy of radiation combined with immune check-point blockade, Twyman-Saint Victor et al. initiated a phase I clinical trial of 22 patients with multiple melanoma metastases. A single index lesion was irradiated with hypofractionated stereotactic body radiation (SBRT; 2-3 doses of 6-8 Gy radiation delivered on separate days), followed by four cycles of the anti-CTLA4 anti-body ipilimumab. Evaluation of the unirradiated lesions by RECIST demonstrated that 18% of patients had a partial response as best response, 18% had stable disease, and 64% had progressive disease. Of note, one patient showed a large reduction in the size of unirradiated tumors and a partial metabolic response by positron emission tomography (PET). None of the 12 patients evaluated by PET had progressive metabolic disease in the irradiated lesion. The median progression-free survival and overall

survival was 3.8 and 10.7 months with median follow-up of 18.4 and 21.3 months (18.0 and 21.3 months for patients without event), respectively.

### 2.7.2 *Radiation in combination with PD-1 blockade*

There are a number of preclinical studies in which radiation has been combined with PD-1 blockade which demonstrate an abscopal effect. Deng et al. reported that radiation in combination with anti-PD-L1 generated an abscopal effect greatly reducing the growth of a secondary unirradiated TUBO flank tumor in murine models (Deng 2014). Rechallenge experiments and tumor rejection in mice suggested the generation of prolonged protective immunity by combined treatment of anti-PD-1 antibodies and radiation. Dovedi et al. showed that radiation combined with anti-PD-1 and anti-PD-L1 antibodies improved long-term survival in murine cancer models and protection against tumor rechallenge (Dovedi 2014). In another example, Park et al. showed abscopal effect of radiation combined with PD-1 blockade in murine melanoma (B16) and renal cell carcinoma models. Of note, the immune-mediated effects of radiation in combination with PD-1 blockade are tumor specific (Park 2015). Radiation of one tumor type (renal cell carcinoma) induced protective immune responses that did not cross over to other tumor types (4T1) in the same mice.

In another model, Sharabi et al. reported that stereotactic radiation induces endogenous antigen-specific immune responses when it is combined with PD-1 checkpoint blockade (Sharabi 2015a). Using a small animal radiation research platform (SARRP), image-guided stereotactic radiation was delivered to B16-OVA melanoma or 4T1-HA breast carcinoma tumors resulting in the development of antigen-specific T cell– and B cell–mediated immune responses. These immune-stimulating effects of stereotactic radiation were significantly increased in combination with PD-1 pathway blockade, resulting in improved local tumor control. Stereotactic radiation is reported to have several effects on the immune system including increasing the percentage of antigen-experienced T cells and effector memory T cells, upregulating tumor-associated antigen–MHC complexes, enhancing antigen cross-presentation in the draining lymph node, and increasing T-cell infiltration into tumors.

### 2.7.3 *The optimal dose and schedule of radiation when combined with immune checkpoint inhibitors*

The optimal fractionation regimen for augmenting immunogenicity of tumors and inducing immune response in patients is unknown (Demaria 2012). In this study, three daily doses of palliative SBRT at 9 Gy per day in a total of 27 Gy will be administered three days (Days −2, −1, and Day 0) prior to the initial administration of study therapy (durvalumab/tremelimumab). The choice of dose and schedule is based on observations by Twyman-Saint Victor et al. (Twyman-Saint Victor 2015) and Sharabi et al. (Sharabi 2015b), that hypofractionated radiation at a dose of 5–20 Gy per fraction is considered to be better than conventionally fractionated schedule of 1.8–2.2 Gy fractions and that concurrent checkpoint blockade starting on the day of or during radiation was better than starting checkpoint blockade after the completion of radiation (Sharabi 2015b).

## 2.8 Rationale for the combination of radiation and dual checkpoint blockade

Twyman-Saint Victor et al. reproduced the synergistic effect of radiation and anti-CTLA4 therapy in mouse models to further characterize the mechanism (Twyman-Saint Victor 2015). Although combined treatment improved responses in irradiated and unirradiated tumors, resistance to the combination therapy was common. Analyses of these mouse models revealed that resistance to the combination of radiation and anti-CTLA4 treatment was due to upregulation

of PD-L1 on tumor cells, resulting in T-cell exhaustion. In an attempt to reduce T-cell exhaustion, the radiation and dual checkpoint blockade with anti-CTLA4 and anti-PD-L1/PD-1 was combined and showed significant synergistic antitumor activity in murine melanoma and pancreatic cancer models (Figure 2) (Twyman-Saint Victor 2015).

Figure 2: PD-1 Blockade Antagonizes Acquired Resistance to Radiation plus anti-CTLA4 Therapy

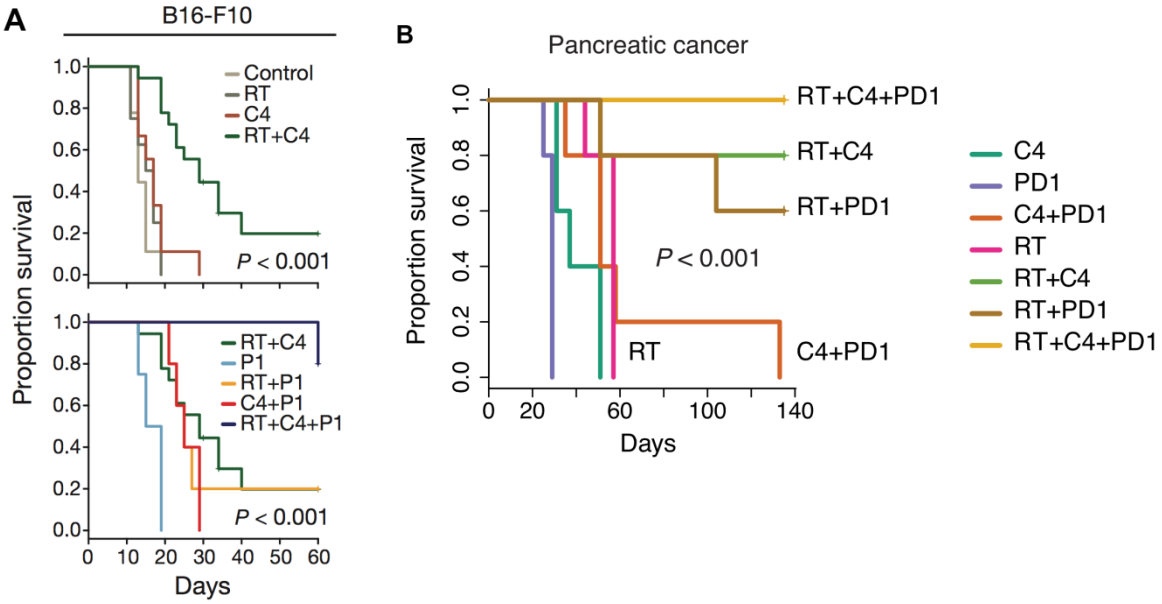



*Figure 2: A*. Survival of mice with B16-F10 tumors (murine melanoma) according to treatment group (N = 18 for RT + C4, N = 5 for others). Shown are overall log-rank P values, Radiation (RT); C4, anti-CTLA4 antibody; PD1, anti-PD-L1.

*B*. Survival of mice with pancreatic tumors from a cell line derived from KPC mice ($Kras^{LSL\text{-}G12D+}$; $p53^{LSL\text{-}R172H+}$; Pdx-1-Cre) (N = 5 for each group). Overall P value is shown.

Further analysis of these murine models (Twyman-Saint Victor 2015) revealed that:

- Anti-CTLA4 predominantly inhibits T-regulatory cells (Treg cells), thereby increasing the $CD8^+$ T-cell to Treg ratio ($CD8^+$/Treg);
- Radiation enhances the diversity of the T-cell receptor (TCR) repertoire of intratumoral T cells; and
- The addition of PD-L1/PD-1 blockade reverses T-cell exhaustion.

Similarly to these results from murine models, melanoma patients with high PD-L1 expression did not respond to radiation plus anti-CTLA4, consistent with persistent T-cell exhaustion (Twyman-Saint Victor 2015). Taken together, this data suggest that the combination of radiation, anti-CTLA4 and anti-PD- L1 may promote antitumor immune response through synergistic mechanisms.

## 2.9 Translational opportunities

Pre-clinical and clinical data suggest that combination of immune checkpoint inhibitors targeting non-overlapping pathways such as durvalumab and tremelimumab may induce synergistic effect leading to improved tumor response in comparison to monotherapy with either agent alone. We hypothesize that the combination of radiation and dual immune checkpoint blockade with durvalumab plus tremelimumab may have synergistic effect on effector T cell activation (Pardoll 2012).

This study serves as a platform allowing for detailed assessment of the mechanisms of immune stimulation, predictive markers of response or resistance and rational development of the next generation of combination immunomodulatory interventions (Taube 2014, Topalian 2012). Samples will be collected that may be used in post-hoc analyses including but, not limited to:

- peripheral lymphocytes analysis for immune cell gene expression and quantitative changes of lymphocyte subpopulation and immune-related cells.
- collection of tumor tissues from unirradiated tumor sites prior to radiation and after two cycles of therapy for further analysis of immune response in tumor.
- analysis of gene expression related to immune checkpoint pathways.
- analysis of frequency of mutation-associated neoantigens in tumor tissues.

## 3.0 STUDY AIMS AND ENDPOINTS

### 3.1 Primary aim and endpoint

*Aim:* To determine the efficacy of the dual immune checkpoint blockade with durvalumab plus tremelimumab following a small dose of hypofractionated palliative radiation in patients with MSS mCRC who have progressed on chemotherapy.

*Endpoint:* Overall objective response rate (ORR) as measured by RECIST 1.1 criteria.

### 3.2 Secondary aims and endpoints

#### 3.2.1 *Clinical benefit rate*

*Aim:* To determine objective tumor decrease and stable disease (SD) at 16 weeks.

*Endpoint:* Measurement of disease status by continuous tumor measurement (any partial response [PR], any complete response [CR] and SD at 16 weeks).

#### 3.2.2 *Duration of response*

*Aim:* To determine the duration of response of mCRC to study therapy.

*Endpoint:* Measurement of time from study entry until documentation of progression as determined by RECIST 1.1.

#### 3.2.3 *Safety and Toxicity*

*Aim:* To determine the safety of the combination of dual immune checkpoint blockade with durvalumab plus tremelimumab following hypofractionated palliative radiation in patients with MSS mCRC who have progressed on chemotherapy.

*Endpoint*: Frequency and severity of adverse events categorized using the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0).

### 3.3 Exploratory Translational Science

*Aim:* To explore the effect of the combination of dual immune checkpoint blockade with durvalumab plus tremelimumab following hypofractionated palliative radiation on immune response in blood and in tumor tissue.

*Aim:* To correlate the frequency of mutation-associated neoantigens in tumor tissues and clinical response.

## 4.0 PATIENT ELIGIBILITY AND INELIGIBILITY

### 4.1 Conditions for patient eligibility

*A patient cannot be considered eligible for this study unless all of the following conditions are met:*

4.1.1 The patient must have consented to participate and, prior to beginning specific study procedures, must have signed and dated an appropriate IRB-approved consent form that conforms to federal and institutional guidelines for study treatment and for submission of tumor and blood samples as required by FC-9 correlative science studies (see Section 6.0***)***.

4.1.2 Patients must be ≥ 18 years old.

4.1.3 The ECOG performance status must be 0 or 1 (see Appendix A).

4.1.4 There must be histologic confirmation of a diagnosis of colorectal adenocarcinoma.

4.1.5 The tumor must have been determined to be microsatellite stable (MSS).

4.1.6 There must be documentation by PET/CT scan, CT scan, or MRI, that the patient has evidence of measurable metastatic disease per RECIST 1.1.

4.1.7 Patients must have an accessible metastatic lesion for pretreatment core biopsy.

4.1.8 Unless either drug is medically contraindicated, patients must have received oxaliplatin and irinotecan as part of standard metastatic chemotherapy regimens.

4.1.9 The patient must have multiple sites of metastatic disease with at least one lesion amenable to treatment with stereotactic radiation therapy (SBRT) in the lung or liver and at least one lesion not being irradiated and meeting RECIST 1.1. (See Appendix B).

4.1.10 At the time of study entry, blood counts performed within 2 weeks prior to study entry must meet the following criteria:

- ANC must be ≥ 1500/mm$^3$,
- Platelet count must be ≥ 100,000/mm$^3$; and
- Hemoglobin must be ≥ 9 g/dL.

4.1.11 The following criteria for evidence of adequate hepatic function performed within 2 weeks prior to study entry must be met***:***

- Total bilirubin must be ≤ 1.5 x ULN (upper limit of normal) for the lab unless the patient has a bilirubin elevation > 1.5 x ULN to 3 x ULN due to Gilbert's disease or similar syndrome involving slow conjugation of bilirubin; *and*
- AST and ALT must be ≤ 2.5 x ULN for the lab *with the following exception:* for patients with documented liver metastases, AST and ALT must be ≤ 5 x ULN.

4.1.12 Adequate renal function within 4 weeks prior to study entry, defined as serum creatinine ≤ 1.5 x ULN for the lab or measured or calculated creatinine clearance > 40 mL/min by Cockcroft-Gault formula**.**

4.1.13 All hematologic, gastrointestinal, and genitourinary chemotherapy toxicities must be < Grade 2 at the time study therapy is to begin. (Note: Transfusions may be used to correct hemoglobin for patients experiencing anemia from therapy who otherwise would be eligible for the study.

4.1.14 Patients with reproductive potential (male/female) must agree to use accepted and highly effective methods of contraception while receiving study therapy and for at least

6 months after the completion of study therapy. The definition of effective method of contraception will be based on the investigator's discretion. See Appendix C.
Female patients must either be of non-reproductive potential (i.e., post-menopausal by history: ≥ 60 years old and no menses for ≥ 1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.

## 4.2 Conditions for patient ineligibility

Any patient with one or more of the following conditions will be ineligible for this study:

4.2.1 Diagnosis of anal or small bowel carcinoma.

4.2.2 Colorectal cancer other than adenocarcinoma, e.g., sarcoma, lymphoma, carcinoid.

4.2.3 Previous therapy with any PD-1 or PD-L1 inhibitor including durvalumab or anti-CTLA4 (including tremelimumab) for any malignancy.

4.2.4 Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving study therapy.

4.2.5 Active or chronic hepatitis B or hepatitis C.

4.2.6 Symptomatic or uncontrolled brain metastases requiring concurrent treatments, uncontrolled spinal cord compression, carcinomatous meningitis, or new evidence of brain or leptomeningeal disease; uncontrolled seizures.

4.2.7 Active infection or chronic infection requiring chronic suppressive antibiotics.

4.2.8 Active or documented inflammatory disease.

4.2.9 Known history of human immunodeficiency virus (HIV) or acquired immunodeficiency-related (AIDS) illnesses.

4.2.10 Current or prior use of immunosuppressive medication within 28 days before the first dose of study therapy with the exceptions of intranasal corticosteroids or systemic corticosteroids at physiological doses that do not exceed 10mg/day of prednisone or an equivalent corticosteroid.

4.2.11 History of allogeneic organ transplantation.

4.2.12 Any of the following cardiac conditions:

- Documented NYHA Class III or IV congestive heart failure,
- Myocardial infarction within 6 months prior to study entry,
- Unstable angina within 6 months prior to study entry,
- Symptomatic arrhythmia.

4.2.13 Uncontrolled high blood pressure defined as systolic BP ≥ 150 mmHg or diastolic BP ≥ 100 mmHg with or without anti-hypertensive medication. Patients with initial BP elevations are eligible if initiation or adjustment of BP medication lowers pressure to meet entry criteria.

4.2.14 Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).

4.2.15 Ongoing or active gastritis or peptic ulcer disease.

4.2.16 Active bleeding diatheses.

4.2.17 Known history of previous diagnosis of tuberculosis.

4.2.18 History of hypersensitivity to durvalumab or tremelimumab or any excipients of these drugs.

4.2.19 Known history or confirmation of active pneumonia, pneumonitis, symptomatic interstitial lung disease, or definitive evidence of interstitial lung disease described on CT scan, MRI, or chest x-ray in asymptomatic patients; dyspnea at rest requiring current continuous oxygen therapy.

4.2.20 Active or prior documented autoimmune disease or inflammatory condition requiring ongoing immunosuppressive medications. (Note: Patients with vitiligo, Grave disease, or psoriasis not requiring systemic treatment within the past 2 years are eligible.)

4.2.21 Other malignancies unless the patient is considered to be disease-free and has completed therapy for the malignancy ≥ 12 months prior to study entry. Patients with the following cancers are eligible if diagnosed and treated within the past 12 months: carcinoma in situ of the cervix, and basal cell and squamous cell carcinoma of the skin.

4.2.22 Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements or interfere with interpretation of study results.

4.2.23 Pregnancy or lactation at the time of study entry. (Note: Pregnancy testing should be performed within 14 days prior to study entry according to institutional standards for women of childbearing potential.)

4.2.24 Use and/or receipt of the last dose of anti-cancer therapy (i.e., chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal anti-bodies) within 14 days prior to the first dose of study therapy. (*Note:* SBRT is required prior to beginning study therapy.)

4.2.25 Use of any investigational agent within 4 weeks of starting study therapy.

## 5.0 REQUIREMENTS FOR STUDY ENTRY, DURING TREATMENT, AND FOLLOW-UP

Tests and exams required before study entry are listed on Table 1. Requirements following study entry are outlined on Table 2.

Table 1. Tests, exams, and other requirements prior to study entry

| Requirements | Prior to Study Entry | |
|---|---|---|
| Consent form for FC-9 signed by the patient | X | |
| Agreement of local Pathology department to release the primary tumor tissue[a] | X | |
| History & physical exam[b] | X | Within 4 weeks |
| Performance status (see Appendix A) | X | |
| Height & weight | X | |
| Sodium, potassium, chloride, bicarbonate or carbon dioxide, calcium, glucose, total protein, LDH | X | |
| Thyroid function tests: TSH[c] | X | |
| Urinalysis | X | |
| CEA | X | |
| PET/CT (if available) **or** CT scan of chest, abdomen, and pelvis with IV/oral contrast (MRI can be substituted for the CT scan)[d] | X | |
| APTT and INR | X | |
| CBC/differential/platelet count | X | Within 2 weeks |
| Total bilirubin (direct and indirect), AST (SGOT), ALT (SGPT), alkaline phosphatase; albumin, lipase, and amylase, creatinine, BUN | X | |
| Pregnancy test[e] | X | |
| Required study blood samples[f] | X | Prior to beginning radiation therapy |
| Core biopsy to procure tumor samples for submission to the NSABP Division of Pathology[g] | X | |

**a** The archived primary tumor tissue from the diagnostic biopsy (or other previous surgery) must be requested and the Pathology department must agree ***before study entry*** to release an archived paraffin tumor block or slides if the block is unavailable (see Section 6.0). Submit the tumor tissue within 60 days after study entry. ***Note****: With confirmation from DSSM, patients whose diagnostic sample was previously submitted for participation in NSABP MPR-1 will have met this study requirement. Provide the MPR-1 Patient ID number to DSSM for confirmation of MPR-1 tumor sample submission.*

**b** Complete H&P by physician or other healthcare professional (on FDA Form 1572).

**c** If TSH abnormal, (outside normal range) obtain free triiodothyronine ($T_3$) and thyroxine ($T_4$).

**d** The same method (PET/CT scan, CT or MRI) used for baseline tumor measurements should be used at all other tumor measurement time points.

**e** For WOCBP: Pregnancy testing should be performed according to institutional standards.

**f** Blood samples collected for research study purposes should be drawn concurrently with blood samples required for study entry. See Section 6.0.

**g** This additional biopsy and overnight submission of fresh tumor samples is a study requirement. See Section 6.0.

***Refer to FC-9 Pathology and Correlative Science Instructions for additional information on blood and tissue collection.***

Table 2. Tests, exams, and other requirements following study entry

| **Required studies** *(see footnote **a**)* | **Within 72 hours before Day 1** (Beginning with Cycle 1 through Cycle 4) *unless indicated otherwise 1 cycle = 28 days* | **Within 72 hours before Day 1** (Beginning with Cycle 5 through Cycle 24) *unless indicated otherwise 1 cycle = 28 days* | **Follow-up** *(Within 30 days following completion or discontinuation of study therapy)* |
|---|---|---|---|
| History & physical exam**a,b** | X | X | X |
| Vital signs**c** | X | X | X |
| Adverse event assessment**b,d** | X | X | X |
| Measurement of target lesions**e** | X (*After Cycles 2 and Cycle 4*) | X (*After every even cycle*) | |
| CBC/differential/platelets | X | X | X |
| Sodium, potassium, chloride, bicarbonate or carbon dioxide, calcium, BUN or urea, creatinine, glucose, total protein | X | X | X |
| Total bilirubin, AST, ALT, alkaline phosphatase; albumin, LDH, lipase, amylase | X | X | X |
| CEA**f** | X (*After every 2 cycles with scans*) | | X |
| TSH**g** | X (*Every 2 cycles*) | X (*Every 2 cycles*) | |
| Urinalysis | X | X | |
| Blood samples**h** | X *(Day 15/Cycle 1 and Day 1/Cycles 2, 4)* | X (*Day 1, Cycle 6*) | |
| Tumor sample**i** | X *(Following completion of Cycle 2) [at 8 weeks]* | | |

*Table 2 continued on next page.*

Table 2. Tests, exams, and other requirements **following study entry** (continued)

| | |
|---|---|
| **a** | At the discretion of the investigator, additional exams, bloodwork, x-rays, ECGs, scans, and other testing may be performed as clinically indicated. |
| **b** | *Note:* Confirmation must be made that resolution of all hematologic, gastrointestinal and genitourinary toxicities are < Grade 2 before beginning the first study therapy infusion. Updated H&P with exams, adverse event assessment, and assessments during therapy and follow-up by physician or other appropriate healthcare professional (on FDA Form 1572). |
| **c** | Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured and recorded. On study therapy treatment days, vital signs will be measured within an hour prior to start of tremelimumab and durvalumab administration, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (+ 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-infusion. If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the time increments as outlined at the end of the infusion or more frequently if clinically indicated. For subsequent doses of study therapy, there will be a 30 minute observation period and vital sign check between tremelimumab and durvalumab doses to monitor potential infusion-related reactions. See Table 4. |
| **d** | AE assessments 90 days (+/− 14 days) after the last dose of study therapy. Should the patient stop study therapy (e.g. due to disease progression or second primary) and begin a new treatment *prior* to the last dose of durvalumab assessment, AE assessments should be collected *only* up to the date the new therapy begins. See Section 10.7. |
| **e** | The same imaging method (PET/CT scan, CT scan or MRI), used at baseline should be used every 2 cycles from start of therapy. Assessment of measurable disease is every 2 cycles by RECIST 1.1. See Section 11.0. |
| **f** | CEA levels should be obtained every 2 cycles to correlate with disease imaging. |
| **g** | If TSH abnormal, (outside normal range) obtain free triiodothyronine ($T_3$) and thyroxine ($T_4$). |
| **h** | Blood samples will be collected on Cycle 1/Day 15, and prior to beginning cycles 2, 4 and 6. Blood samples collected for research study purposes should be drawn concurrently with blood samples required for study. See FC-9 Pathology and Correlative Science Instructions for required correlative study blood collection instructions. See Section 6.0. |
| **i** | Submission of core biopsy specimens of an accessible metastatic lesion collected after completion of cycle 2 (approximately 8 weeks) is a study requirement. |
| ***NOTE: Refer to the FC-9 Pathology and Correlative Science Instructions for tumor and blood sample submission instructions.*** | |

## 6.0 PATHOLOGY AND CORRELATIVE SCIENCE STUDIES

### 6.1 Overview of requirements

Collection and submission of all patient samples (blood, tumor) as listed below is a requirement for all patients participating in the NSABP FC-9 study. ***By signing the FC-9 consent form, the patient has agreed to all required sample collections and submissions.***
Non-submission of required patient samples will be a protocol violation.

Table 3. Summary of FC-9 patient sample submission requirements

| **Study Requirements for ALL Patients** *(unless indicated otherwise)* | **Prior to Study Entry** | **Before radiation therapy begins** *(Prior to Day −2)* | **Cycle 1, Day 15** | **Up to 3 days prior to Day 1 of Cycles 2, 4 and 6 Therapy Begins** |
|---|---|---|---|---|
| **Submission of treatment-naive tumor (primary or metastatic diagnostic tumor [FFPE block])** | Yes[a] | N/A | | N/A |
| **Submission of fresh tumor samples[b]** | Yes | | | Yes *(Following completion of cycle 2 [at 8 weeks])* |
| **Collection & submission of blood samples[c]** | Yes | | Yes | Yes |

**a** Archived paraffin block of primary tumor tissue is preferable. Refer to FC-9 Pathology and Correlative Science Instructions for acceptable alternative submissions.
*Note: After confirmation by DSSM, patients whose diagnostic sample was previously submitted for participation in NSABP MPR-1 will have met this study requirement. Provide the MPR-1 Patient ID number to DSSM for confirmation of MPR-1 tumor sample submission.*

**b** Submission of core biopsy specimens of an accessible metastatic lesion collected prior to beginning radiation therapy and following completion of Cycle 2 (at 8 weeks on study therapy) is a study requirement.

**c** Blood sample collections: Pre-treatment *prior* to beginning radiation therapy, Day 15 of Cycle 1, and Day 1 of Cycles 2, 4, and 6. See Section 6.3.2.

***Refer to the FC-9 Pathology and Correlative Science Instructions for tumor and blood sample submission instructions.***

### 6.2 Use of specimens

The blood and tumor samples collected in this study will be used for FC-9 studies as described in Section 6.4 and for analyses to be conducted in the future related to the purposes of the FC-9 study but not currently described in the protocol. Additionally, the specimens procured may be used for future studies involving gene and proteins conferring susceptibility to cancer or other diseases. Results of the correlative science studies, including raw sequencing data, will not be reported directly to the patient or the physician and will not have any bearing on patient treatment.

The results of the study will be communicated through publication, in peer reviewed scientific literature and/or through presentations at scientific meetings. However, anonymized or de-identified research data (as deemed appropriate by the NSABP), including genome sequencing data, may be submitted to public research databases for data sharing with scientific researchers outside of the NSABP.

## 6.3 Required tumor and blood sample submission procedures

### 6.3.1 *Archived primary tumor tissue*

Submission of archived primary tumor block prepared from the diagnostic biopsy or other surgery is a study requirement. If the tumor block is not available, refer to FC-9 Pathology and Correlative Science Instructions for details on alternative submission.

Note: After confirmation by DSSM, patients whose diagnostic sample was previously submitted for participation in NSABP MPR-1 will have met this study requirement. Provide the MPR-1 Patient ID number to DSSM for confirmation of MPR-1 tumor sample submission.

### 6.3.2 *Study blood samples*

Blood samples will be collected and submitted at 5 time points for each patient:
- Pre-treatment (*prior* to beginning radiation therapy),
- Cycle 1, Day 15
- Cycle 2, Day 1;
- Cycle 4, Day 1, and
- Cycle 6, Day 1.

### 6.3.3 *Fresh tissue collection*

Required tumor samples will be collected at 2 time points for each patient:
- At pre-treatment prior to radiation; and
- After Cycle 2 (8 weeks).

## 6.4 Correlative Science Studies

The following correlative science studies are planned to determine the effect of the combination of radiation and dual immune checkpoint blockade with durvalumab plus tremelimumab on immune response in blood and in tumor tissues.

### 6.4.1 *Immune monitoring of peripheral blood*

- Blood lymphocytes may be analyzed for immune cell gene expression and quantitative changes of lymphocyte subpopulation and immune-related cells prior to radiation and while receiving study therapy.
- Peripheral blood mononuclear cells (PBMC) may be assessed by fluorescence-activated cell sorting (FACS) or with gene expression for changes in cell subsets including, but not limited to, naive and memory $CD8^+$ and $CD4^+$ T cells, MDSCs, NK, and B cells. The PBMCs may be used to screen for immune response and for functional assays such as an assessment of antibody dependent cell mediated cytotoxicity (ADCC).

### 6.4.2 *Analysis of circulating tumor DNA and circulating tumor cells*

Peripheral blood mononuclear cells (PBMCs) may also be archived to isolate circulating tumor cells (CTCs) and/or cell free DNA (cfDNA). The cfDNA may be used to profile circulating tumor DNA for mutations, amplifications, gene fusions or other genetic

abnormalities arising during the course of disease or in response to therapy. Analyzing detected cfDNA and CTCs in PBMC may provide further understanding of patient response and explain resistance or sensitivity to therapy.

6.4.3 ***Analysis of tumor infiltrating immune cell populations***

It is expected that immunogenic cell death of cancer cells induced by radiation of an index lesion enhance antitumor immune response. Tumor tissues from unirradiated tumor sites will be procured at baseline prior to radiation and after cycle 2 for further analysis of immune response in tumor. The extent of intratumoral $CD8^+$ T and other immune cell infiltrates in tumor tissues may be analyzed and the immunoscore may be determined as reported previously (Tumeh 2014, Galon 2006, Pages 2005, Llosa 2015). We will use the most appropriate technology at that time.

The tumor/immune microenvironment may be assessed by IHC staining of multiple immune markers utilizing the PerkinElmer's opal-7 color staining system and their Vectra® quantitative pathology imaging systems with the inForm® Advanced Image Analysis system. Multiplex staining of up to 6 different markers enables the identification of helper B cells (CD20), T cells (CD4), cytotoxic T cells (CD8), memory T cells (CD45RO) and regulatory T-cells (FOXP3) in a single section of tissue. Other markers such as PD-L1, PD-1 can also be multiplexed with these immune markers. This allows for not only the quantification of specific types of immune cells but also localizes these cells with respect to the tumor and with respect to each other, an important consideration for assessment of the immune environment.

6.4.4 ***Analysis of gene expression involved in immune checkpoint pathways in tumor tissues***

It is known that multiple immune checkpoint pathways are involved in antitumor immune response. Expression of genes involved in immune checkpoint pathways including PD-L1/2, LAG-3, OX40, GITR, TIM-3, CD137, IDO, markers for MDSCs, and markers associated with immunogenic cell death (Bezu 2015) may be analyzed by IHC in tumor tissue biopsied at pre-treatment prior to radiation and after cycle 2 (8 weeks) (Tumeh 2014, Llosa 2015). RNA-Seq and/or the nCounter Vantage™ RNA: Protein Immune Cell profiling panel from NanoString which interrogates the expression of 770 genes and 30 proteins may be used to assess the expression of both the tumor and immune microenvironment.

6.4.5 ***Analysis of the frequency of mutation-associated neoantigens in tumor tissues***

It has been shown that the frequency of mutation-associated neoantigens in tumor tissues correlates with clinical response to immune checkpoint inhibitors in melanoma, lung cancers and MSI-high colorectal cancer (Le 2015, Alexandrov 2013, Snyder 2014, Rizvi 2015). The frequency of mutation-associated neoantigens in tumor tissues may be analyzed for any significant correlation with clinical response to the study treatment (Le 2015, Vogelstein 2013, Alexandrov 2013, Snyder 2014, Yadav 2014, Rizvi 2015).

6.4.6 ***Proteomic analysis of signaling pathways***

Protein lysates generated from archived tissue may be used to interrogate signaling pathways using microarrays or related technologies depending on the state of the art at the time these experiments are undertaken. High throughput assays (such as Reverse Phase Protein Microarrays-RPPA for example) allow simultaneous evaluation of the activation status of multiple signaling pathways, by probing for protein phosphorylation, expression levels and other related parameters. Analyzing such changes may provide further understanding of patient response and explain resistance or sensitivity to therapy.

## 7.0 TREATMENT REGIMEN

Study therapy (Cycle 1/Day1) should begin following three doses of 9 Gy hypofractionated SBRT to a single index lesion on Day – 2, Day −1, and Day 0 *prior* to Cycle 1.

The lesion selected for radiation should be a lesion that can be safely radiated with focal irradiation (SBRT) for which radiation at the limited, palliative doses contemplated would be considered medically appropriate and in accord with acceptable radiation oncology practice. For SBRT guidance, see Appendix B.

### 7.1 Study therapy

Note: See Section 9.0 for specific study drug information and preparation instructions. Study therapy must be administered in the order outlined in Table 4. See Table 7 for study therapy dose level management.

Table 4. Study therapy (tremelimumab and durvalumab)

| Drug | Dose | Administration | Dosing Interval | Planned Duration |
|---|---|---|---|---|
| ***Cycles 1–4*** | | | | |
| **Tremelimumab[a,c,d]** | 75 mg | IV infusion *(See footnotes **a and c** for administration instructions)* | 1 dose every 4 weeks on Day 1 of cycles 1, 2, 3 and 4 (*1 cycle = 4 weeks*) | 4 cycles |
| **Durvalumab[b,c,d]** | 1500 mg | IV infusion *(See footnotes **b and c** for administration instructions)* | 1 dose every 4 weeks on Day 1 of cycles 1, 2, 3 and 4 *(1 cycle = 4 weeks)* | 4 cycles |
| ***Cycles 5-24*** | | | | |
| **Durvalumab[b,c,d]** | 1500mg | IV infusion *(See footnotes **b and c** for administration instructions)* | 1 dose every 4 weeks on Day 1 of cycles 5 through 24 *(1 cycle = 4 weeks)* | 20 cycles |

*Table 4 continued on next page.*

Table 4. Study therapy (tremelimumab and durvalumab) *(continued)*

**a** ***Tremelimumab*** will be administered as a controlled IV infusion using a low protein binding 0.2 or 0.22 µm in-line filter via infusion pump into peripheral or central venous access. See Section 9.1.

- The entire contents of the IV bag should be administered over 60 minutes (+/– 5 minutes) at room temperature (approximately 25˚C).
- In the event of a ≤ Grade 2 infusion reaction, the infusion rate may be decreased or interrupted until resolution of the event and re-initiated at 50% of the initial infusion rate. Subsequent infusions may be administered at 50% of the initial infusion rate.
- The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 8 hours at room temperature, (otherwise requires new infusion preparation).
- Following completion of the tremelimumab infusion, flush the IV line with a volume of IV solution equal the volume contained in the tubing or complete the infusion according to institutional policy to assure the full dose is administered.

*Note:* A one hour observation period is required between the **first** dose of tremelimumab and durvalumab and after the first dose of durvalumab. See Table 2. For subsequent doses a 30 minute observation period is recommended between tremelimumab and durvalumab and after durvalumab. See Table 2.

**b** ***Durvalumab*** will be administered as a controlled IV infusion using a low protein binding 0.2 or 0.22 µm in-line filter via infusion pump into peripheral or central venous access. See Section 9.2.

- On Day 1 of Cycles 1, 2, 3 and 4, durvalumab will be administered approximately 1 hour ***after*** the completion of the tremelimumab IV infusion. Durvalumab (Day 1 of Cycles 5 through and including 24) will be administered as monotherapy.
- The entire contents of the IV bag should be administered over 60 minutes (+/– 5 minutes) at room temperature (approximately 25˚C).
- In the event of a ≤ Grade 2 infusion reaction, the infusion rate may be decreased or interrupted until resolution of the event and re-initiated at 50% of the initial infusion rate. Subsequent infusions may be administered at 50% of the initial infusion rate.
- The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 8 hours at room temperature, with maximum total time at room temperature not exceeding 8 hours (otherwise requires new infusion preparation).
- Following completion of the durvalumab infusion, flush the IV line with a volume of IV solution equal the volume contained in the tubing or complete the infusion according to institutional policy to assure the full dose is administered.

**c** Vital Signs will be measured within an hour *prior* to start of tremelimumab and durvalumab administrations, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (+ 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-infusion. If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the time increments as outlined at the end of the infusion or more frequently if clinically indicated. For subsequent doses of study therapy, a 30 minute observation period and vital sign check is required unless a patient experiences an infusion-related reaction and requires additional monitoring.

**d** ***Allergic reactions to durvalumab and tremelimumab are possible.*** See Sections 8.5.1 and 8.5.2.

- A 1-hour observation period is required following the ***first*** infusion of both study drugs.
- Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator.
- The infusion rate of study drug may be decreased by 50% or interrupted as described above
- 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.

## 7.2 Supportive therapy

### 7.2.1 *Growth factor support*

Use of growth factor support (e.g., G-CSF, GM-CSF) is prohibited.

### 7.2.2 *Erythropoietin*

The use of erythropoiesis-stimulating agents is prohibited.

### 7.2.3 *Other supportive care*

Patients should receive supportive care for other treatment-related symptoms at the investigator's discretion.

### 7.2.4 *Targeted therapy*

While on study, administration of targeted therapy for malignancy is prohibited.

## 7.3 Contraindications and precautions

- Study therapy, durvalumab and tremelimumab is contraindicated in patients who are pregnant or lactating. See Section 10.5 and Appendix C.
- Immunosuppressive doses of steroids or other immunosuppressive medications through 90 days post last dose of study therapy. See 4.2.10. Note however, use of immunosuppressive medications for the management of study therapy-related AEs (see Section 8.5) or in patients with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted.
- Drugs with laxative properties and herbal or natural remedies for constipation should be avoided through 90 days post last dose during the study because of the potential for exacerbation of diarrhea.
- Live attenuated vaccinations during the study or up to 180 days following the last dose of investigational product.
- Patients should not donate blood while participating in this study or for at least 180 days following the last infusion of study therapy.

## 7.4 Participation in other clinical trials

If a patient on the FC-9 trial is considering participation in another clinical trial (including supportive therapy trials), contact the DSSM (see Information Resources.)

## 8.0 TREATMENT MANAGEMENT

### 8.1 General instructions

- The NCI CTCAE v4.0 must be used to grade the severity of AEs.
- All treatment decision must be based on the AE requiring the greatest modification.
- Drug doses that have been reduced may not be re-escalated.
- All hematologic, gastrointestinal, and genitourinary toxicities must be < Grade 2 prior to initiating Dose 1 of study therapy. Patients unable to receive Dose 1 will be considered screen failures.

### 8.2 Treatment management for durvalumab and tremelimumab

The study treatment schedule should be maintained. If necessary, the timing of a treatment may be adjusted to 3 days earlier or 3 days later than the scheduled date of treatment. All doses administered or missed must be recorded.

#### 8.2.1 *Treatment decisions when therapy must be held*

- In the event systemic steroid therapy is initiated for toxicity management, study therapy must be held. The steroid taper should be completed within 28 days. Study therapy may then be resumed after completion of the steroid taper on Day 1 of the next scheduled cycle.
- Note: Should the steroid taper require a slower rate for completion (i.e., > 28 days), further study therapy doses must be discontinued.
- See Table 7 for treatment management.

#### 8.2.2 *Treatment decisions when therapy must be discontinued*

Treatment must be discontinued if:

- If either durvalumab or tremelimumab must be held for > 28 days of continuous delay for other than steroid taper (e.g., toxicity).
- Consent is withdrawn or patient is lost to follow-up. If consent is withdrawn, the patient will not receive any further investigational product or further study observation.
- An adverse event occurs that, in the opinion of the investigator or sponsor, contradicts further dosing.
- The patient becomes pregnant or intends to conceive a child while actively on study.
- Grade 3 or greater infusion reaction occurs.
- Bullous rash.
- Diagnosis of Guillain-Barre and/or Myasthenia Gravis.
- Initiation of alternate cancer therapy including another investigational agent.
- If tumor progression occurs during study therapy, durvalumab must be discontinued. See Section 11.0.

See Table 7 for additional treatment management requirements. Patients who prematurely discontinue study therapy should complete assessments on Table 2.

### 8.3 Dose modifications for durvalumab and tremelimumab

The instructions for management of toxicities during durvalumab and tremelimumab are outlined in Table 7. Dosing of study therapy will be done in tandem:

- When study therapy doses are to be maintained, **both** durvalumab and tremelimumab doses will be maintained on the same dose level.

- When a dose reduction is indicated, **both** durvalumab and tremelimumab will be reduced to the same dose level (e.g., Dose level 1).
- When discontinuation of study therapy is indicated, durvalumab and tremelimumab will be discontinued at the same time.

Table 5. Dose levels for durvalumab

| **Durvalumab** | **Dose Level 0** ***Starting Dose*** | **Dose Level −1** | **Dose Level −2** |
|---|---|---|---|
| | 1500 mg | 750 mg | Discontinue |

Table 6. Dose levels for tremelimumab

| **Tremelimumab** | **Dose Level 0** ***Starting Dose*** | **Dose Level −1** | **Dose Level −2** |
|---|---|---|---|
| | 75 mg | 40 mg | Discontinue |

## 8.4 Dose modification and management of toxicities

All toxicities will be graded according to CTCAE version 4.0. Following the first dose of durvalumab and tremelimumab, subsequent administration of durvalumab and tremelimumab can be modified based on toxicities observed as described in Sections 8.5, 8.6, and 8.7. For adverse events (AEs) that are considered at least partly due to administration of durvalumab or tremelimumab, the following general guidance may be applied:

- Treat each of the toxicities with maximum supportive care (including holding the study therapy suspected of causing the toxicity where required).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.
- In addition to the criteria for permanent discontinuation of study therapy based on toxicity grade, permanently discontinue study therapy for the conditions outlined in Section 8.2.2.

Table 7. Treatment management for study therapy (durvalumab and tremelimumab)

| CTCAE v4.0 Adverse Event | CTCAE v4.0 Grade | Action to be Taken with Study Therapy | |
|---|---|---|---|
| | | Tremelimumab | Durvalumab |
| **Cardiac Disorders** | | | |
| **Myocarditis** *(See Sections 8.5.1 and 8.5.12)* | 1 | For suspected myocarditis: Hold study therapy until full diagnostic work up. Initiate steroid therapy and appropriate management. If study therapy is held, resume after complete resolution to Grade 0 after completion of the steroid taper, *resume at the next scheduled dose*. | |
| | 2 | Hold study therapy dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then: The decision to reinitiate study therapy will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently: *Discontinue study therapy.* | |
| | 3-4 | *Discontinue study therapy* | |
| **Endocrine disorders** | | | |
| **Endocrinopathy** *(e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)* *(See Sections 8.5.1 and 8.5.8)*. | 1 | No dose modifications. | |
| | 2 | 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 and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). Hold study therapy dose until patient is clinically stable. − If systemic steroid therapy has been initiated − after completion of the steroid taper, resume. − If steroid taper completion is > 28 days: discontinue further study therapy. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study therapy on the following conditions: − The event stabilizes and is controlled. − The patient is clinically stable as per investigator or treating physician's clinical judgement. − Doses of prednisone are ≤10 mg/day or equivalent. | |

*Table 7 continued on next page.*

Table 7. Treatment management for study therapy *(continued)*

| CTCAE v4.0 Adverse Event | CTCAE v4.0 Grade | Action to be Taken with Study Therapy | |
|---|---|---|---|
| | | **Tremelimumab** | **Durvalumab** |
| **Endocrine disorders (continued)** | | | |
| **Endocrinopathy** *(e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)* *(See Sections 8.5.1 and 8.5.8).* | 3-4 | 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 and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones).<br>Hold study therapy dose until patient is clinically stable.<br>– If systemic steroid therapy has been initiated – after completion of the steroid taper, resume study therapy.<br>– If steroid taper completion is > 28 days: discontinue further study therapy.<br>Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study therapy on the following conditions:<br>– The event stabilizes and is controlled.<br>– The patient is clinically stable as per investigator or treating physician's clinical judgement.<br>Doses of prednisone are ≤10 mg/day or equivalent. | |
| **Gastrointestinal disorders** | | | |
| **Diarrhea/Enterocolitis** *(See Sections 8.5.1 and 8.5.4.)* | 1 | *Maintain study dose schedule without delay*; adjust antidiarrheal medication. | |
| | 2 | Hold study therapy and adjust antidiarrheal medication. Once event is stabilized to ≤ Grade 1 after completion of the steroid taper, then resume:<br>↓ *one dose level.*<br>If steroid taper completion is > 28 days: *Discontinue further study therapy.* | |
| | 3 | Hold study therapy and adjust antidiarrheal medication. If event is stabilized to ≤ Grade 1 within 14 days, after completion of the steroid taper, resume:<br>↓ *one dose level.*<br>If there is no improvement within 14 days or steroid taper completion is > 28 days:<br>*Discontinue further study therapy.* | |
| | 4 | *Discontinue study therapy* | |
| **Hepatobiliary Disorders** | | | |
| **Hepatitis/hepatotoxicity** *(See Sections 8.5.5, 8.6.2, and 8.7.)* | 3, 4 | *Discontinue study therapy* | |

*Table 7 continued on next page.*

Table 7. Treatment management for study therapy *(continued)*

| CTCAE v4.0 Adverse Event | CTCAE v4.0 Grade | Action to be Taken with Study Therapy | |
|---|---|---|---|
| | | **Tremelimumab** | **Durvalumab** |
| **Immune System Disorders** | | | |
| **Allergic reaction/ Infusion reaction** *(See Table 4 and Sections 8.5.1 and 8.5.2.)* | 1 | The infusion rate of study therapy may be decreased by 50% or temporarily interrupted until resolution of the event. *Maintain study dose level.* | |
| | 2 | The infusion rate of study therapy may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate. Once event is stabilized to ≤ Grade 1, after completion of the steroid taper, resume: ↓ *one dose level.* If steroid taper completion is > 28 days: *Discontinue further study therapy.* | |
| | 3,4 | *Discontinue study therapy* | |
| **Investigations** | | | |
| ***Immune-mediated hepatitis as indicated by:*** • **Alanine transferase (ALT) increased** • **Alkaline phosphatase increased** • **Aspartate aminotransferase (AST) increased** • **Blood bilirubin increased** *Note: Permanently discontinue study therapy for any case meeting Hy's Law criteria. (See Sections 8.5.5, 8.6.2, and 8.7[Hy's Law].)* | 1 | Monitor LFTs; *Maintain study dose level.* | |
| | 2 | *Note: For patients with metastatic liver disease who enter the study with Grade 2 transaminases: Maintain dose and continue study therapy without holding. Otherwise:* | |
| | | Hold study therapy. Once elevations have resolved to ≤ Grade 1 and, • No systemic steroid therapy has been initiated then resume: *Maintain dose level* • Systemic steroid therapy has been initiated − after completion of the steroid taper, resume: ↓ *one dose level or discontinue*. • If steroid taper completion is > 28 days: *Discontinue further study therapy*. | |

*Table 7 continued on next page.*

Table 7. Treatment management for study therapy *(continued)*

| CTCAE v4.0 Adverse Event | CTCAE v4.0 Grade | Action to be Taken with Study Therapy | |
|---|---|---|---|
| | | **Tremelimumab** | **Durvalumab** |
| **Investigations *(continued)*** | | | |
| ***Immune-mediated hepatitis as indicated by:***<br>• **Alanine transferase (ALT) increased**<br>• **Alkaline phosphatase increased**<br>• **Aspartate aminotransferase (AST) increased**<br>• **Blood bilirubin increased**<br>*Note: Permanently discontinue study therapy for any case meeting Hy's Law criteria.*<br>*(See Sections 8.5.5, 8.6.2, and 8.7[Hy's Law].)* | 3 | *Elevations in transaminases ≤ 8 x ULN and bilirubin ≤ 5 x ULN:*<br>Hold study therapy; if elevations resolve to ≤ Grade 1 or base line *within 14 days*, and if<br>• no systemic steroid therapy has been initiated: then resume:<br>*Maintain dose or↓ one dose level.*<br>• systemic steroid therapy has been initiated − after completion of the steroid taper, resume:<br>*↓ one dose level or discontinue.*<br>• If steroid taper completion is > 28 days: *discontinue*.<br>*Note:* If elevations do not downgrade to ≤ Grade 1 within 14 days **OR** for elevations in transaminases > 8 x ULN or bilirubin >5 x ULN*: Discontinue further study therapy.*<br>Discontinue study therapy for any case meeting Hy's law criteria and in the absence of any alternative cause. | |
| | 4 | *Discontinue study therapy* | |
| **Creatinine increased** *(Nephritis)*<br>*(See Sections 8.5.1 and 8.5.6.)* | 1 | Maintain study dose level | |
| | 2 | Hold study therapy until resolved to ≤ Grade 1 after completion of the steroid taper, resume:<br>*↓ one dose level.*<br>If steroid taper completion is > 28 days: *Discontinue further study therapy*. | |
| | 3, 4 | *Discontinue study therapy* | |
| **Platelet count decreased** *(See Section 8.5.11.)* | 2 | *Hold until ≤ Grade 1 or baseline,* then resume and: *Maintain dose or ↓ one dose level*. | *Hold until ≤ Grade 1 or baseline,* then resume and: *Maintain dose* |
| | 3 | *Hold until ≤ Grade 1 or baseline,* then resume and: *↓ one dose level*. | *Hold until ≤ Grade 1 or baseline,* then resume and: *Maintain dose* |
| | 4 | *Discontinue study therapy* | |
| **Musculoskeletal and connective tissue disorders** | | | |
| **Myositis/Polymyositis** *(See section 8.5.13)* | 1 | No dose modifications. | |
| | 2 | Hold study therapy dose until resolution to Grade ≤1. Discontinue study therapy if it does not resolve to Grade ≤1 within 28 days or if there are signs of respiratory insufficiency. | |
| | 3 | Hold study therapy dose until resolution to Grade ≤1. Discontinue study therapy if Grade 3 imAE does not resolve to Grade ≤1 within 28 days or if there are signs of respiratory insufficiency. | |
| | 4 | *Discontinue study therapy* | |

*Table 7 continued on next page.*

Table 7. Treatment management for study therapy *(continued)*

| CTCAE v4.0 Adverse Event | CTCAE v4.0 Grade | Action to be Taken with Study Therapy | |
|---|---|---|---|
| | | **Tremelimumab** | **Durvalumab** |
| **Nervous system disorders** | | | |
| **Neurotoxicity** *(to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)* *(See Sections 8.5.1 and 8.5.9.)* | 1 | Hold study therapy during neurotoxicity work-up. If diagnosis of Myasthenia Gravis or Guillain-Barre is confirmed, discontinue study therapy. *Otherwise, maintain study dose level.* | |
| | 2,3 | Hold study therapy during neurotoxicity work-up. Once elevations have resolved to ≤ Grade 1, and if<br>• no systemic steroid therapy has been initiated, then resume:<br>↓ *1 dose level.*<br>• systemic steroid therapy has been initiated −after completion of the steroid taper: *resume*<br>↓ *1 dose level or discontinue* If steroid taper completion is > 28 days: *discontinue further study therapy.* | |
| | 4 | *Discontinue study therapy* | |
| **Peripheral neuromotor syndrome** *(such as Guillain-Barre and myasthenia gravis)* *(See Sections 8.5.1 and 8.5.10.)* | 1 | No dose modifications. | |
| | 2 | Hold study therapy dose until resolution to Grade ≤1. Permanently discontinue study therapy if it does not resolve to Grade ≤1 within 28 days or if there are signs of respiratory insufficiency or autonomic instability. | |
| | 3 | Hold study therapy dose until resolution to Grade ≤1. Permanently discontinue study therapy if it does not resolve to Grade ≤1 within 28 days or if there are signs of respiratory insufficiency or autonomic instability. | |
| | 4 | *Discontinue study therapy* | |
| **Respiratory, thoracic, and mediastinal disorders** | | | |
| **Pneumonitis/pulmonary infiltrates/other pulmonary events**<br>• ***Dyspnea***<br>• ***Hypoxia***<br>• ***Pneumonitis***<br>• ***ILD***<br>• ***Pulmonary fibrosis***<br>*(See Sections 8.5.1, 8.5.3, and 8.6.1.)* | *Hold study treatment until pneumonitis is evaluated.* | | |
| | 1 | *Maintain* study therapy schedule without delay. | |
| | 2 | Hold study therapy. At physician's discretion, once event is stabilized to ≤ Grade 1 after completion of the steroid taper, then resume*:*<br>↓ *one dose level.*<br>If steroid taper completion is > 28 days: *discontinue further study therapy.* | |
| | 3,4 | *Discontinue study therapy* | |

*Table 7 continued on next page.*

Table 7. Treatment management for study therapy *(continued)*

| CTCAE v4.0 Adverse Event | CTCAE v4.0 Grade | Action to be Taken with Study Therapy | |
|---|---|---|---|
| | | **Tremelimumab** | **Durvalumab** |
| **Skin and subcutaneous tissue disorders** | | | |
| **Rash/dermatitis** *(e.g., acneiform, maculo-papular)* *(See Sections 8.5.1 and 8.5.7.)* | 1 | Maintain dose level | |
| | 2 | Hold study therapy until resolution to ≤ Grade 1 or baseline and if<br>• no systemic steroid therapy has been initiated−resume: *Maintain dose level* or ↓ *one dose level.*<br>• systemic steroid therapy has been initiated −after completion of the steroid taper: *Maintain dose level or ↓ one dose level.*<br>If steroid taper completion is > 28 days: *discontinue further study therapy.* | |
| | 3 | Hold study therapy until resolution to ≤ Grade 1 or baseline and if<br>• no systemic steroid therapy has been initiated−resume: ↓ *one dose level or discontinue.*<br>• systemic steroid therapy has been initiated −after completion of the steroid taper: ↓ *one dose level or discontinue.*<br>If steroid taper completion is > 28 days: *Discontinue further study therapy.* | |
| | 4 | *Discontinue study therapy* | |
| **Rash** *(e.g., bullous skin formations)* *(See Section 8.5.7)* | All Grades | *Discontinue study therapy* | |
| **AEs of Non-Immune Mediated Reactions** | | | |
| **AEs of non-immune mediated reaction requiring dose modification per investigator** *(e.g., Section 8.5.1)* | 1 | Maintain dose | |
| | 2 | Hold study therapy until resolution to ≤ Grade 1 or baseline then resume: *Maintain dose* or ↓ *one dose level*. | |
| | 3 | Hold study therapy until resolution to ≤ Grade 1 or baseline, then resume: ↓ *one dose level* or *discontinue at physician's discretion*. | |
| | 4 | *Discontinue study therapy* | |

## 8.5 Immune-mediated adverse events (imAEs)

Immune-mediated adverse events/imAEs are important risks of interest and include: pneumonitis/ interstitial lung disease (ILD), diarrhea/colitis, hepatitis and increases in transaminases, nephritis and increases in serum creatinine, dermatitis/rash and pruritus, endocrinopathy (hypo- and hyperthyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type I diabetes mellitus), myocarditis, neuropathy/neuromuscular toxicity (such as myasthenia gravis and Guillain-Barre) and pancreatitis. In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacologic etiology are also considered AESIs. See Section 10.2.

Other inflammatory responses that are rare with a potential immune related etiology are also considered as AESIs and include but are not limited to pericarditis, sarcoidosis, uveitis, and other events involving the eye, skin, hematological and rheumatological events. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs (Durvalumab IB 2018).

Thorough evaluation of these events should be performed to rule out any alternative etiology (e.g., disease progression, concomitant medications, or infections). In the absence of a clear alternative etiology, all events should be considered potentially immune related. For study treatment dose management related to imAEs, see Table 7.

The following guidelines are *recommended* as management of the following immune-mediated reactions.

8.5.1 ***Overall management for imAEs***

- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.).
- In the absence of a clear alternative etiology, all events should be considered potentially immune related.
- Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events.
- For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥ 3) events promptly start prednisone 1-2mg/kg/day PO or IV equivalent unless otherwise noted in subsequent sections.
- Some 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 – 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. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation.
- If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g. up to 2-4 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).
- More potent immunosuppressives such as TNF inhibitors (e.g. infliximab) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in 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 these events are not responding to systemic steroids.
- With long-term steroid and other immunosuppressive use, consider need for Pneumocystis jirovecii pneumonia (PJP, formerly known as Pneumocystis carinii pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring.
- Discontinuation of study therapy is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study therapy in this situation should be based upon a benefit-risk analysis for that patient.

***Note:*** Non-imAEs should be treated as per institutional standard.

8.5.2 ***Infusion reactions***

Management of reactions should be 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.). See Section 8.5.1 and Table 7.

The following are recommended management practices for infusion reactions:

- *Grade 1*:
  - The infusion rate of study therapy may be decreased by 50% or temporarily interrupted until resolution of the event.
  - 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.

Note: Steroids should not be used for routine premedication of < Grade 2 infusion reactions.

- *Grade 2*:
  - The infusion rate of study drug may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.
  - 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.
  - Report event to DSSM.
- *Grade 3 and 4*:
  - Permanently discontinue study therapy.
  - Report event to DSSM.

Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

### 8.5.3 ***Pneumonitis/ILD***

Monitor patients for signs and symptoms of pneumonitis or interstitial lung disease (ILD) (e.g., new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests including other diagnostic procedures. Prompt treatment with steroids is important per guidelines below.

- Patients should be instructed to call the clinic to report any respiratory symptoms or changes they experience including:
  - cough
  - shortness of breath
  - dyspnea upon exertion
  - fever, and/or
  - chest pain.

For study treatment dose management related to imAEs, see Section 8.5.1 and Table 7.

- *Grade 1*:
  - 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.
  - Consider holding study therapy as clinically appropriate and during diagnostic workup for other etiologies.

- *Grade 2*:
  - Hold study therapy until Grade 2 resolution to ≤ Grade 1.
  - Monitor symptoms daily and consider hospitalization.
  - Promptly start systemic steroids (e.g., prednisone 1-2 mg/kg/day PO 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.
  - If still no improvement within 3-5 days despite IV methylprednisolone at 2-4/g/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, if administered, refer to infliximab label for general guidance.
  - Once improving, gradually taper steroids (28 days of taper) and consider prophylactic antibiotics, antifungal or anti-pneumocystis pneumonia (PJP) treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
  - Consider Pulmonary and Infectious Disease consult.
  - Consider as necessary discussing with study physician.
  - Report event to DSSM.
- *Grade 3 or 4*:
  - Discontinue study therapy.
  - 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.).
  - Report event to DSSM.
  - If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors started (e.g., infliximab at 5 mg/kg every 2 week dose). *Caution:* It is important to rule out sepsis and, if administered, refer to infliximab label for general guidance.
  - Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and in particular, anti PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).

### 8.5.4 ***Diarrhea/enterocolitis***

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. For study treatment dose management related to imAEs, see Section 8.5.1 and Table 7.

- *Grade 1*:
  *(Diarrhea: stool frequency of <4 over baseline per day; Colitis: asymptomatic; clinical or diagnostic observations only)*
  - 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 frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)*
  - Hold study therapy until resolution to Grade ≤ 1.
  - 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 PO or IV equivalent.
  - If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, obtain GI consult for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4 mg/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). Caution: Important to rule out bowel perforation and, if administered, refer to infliximab label for general guidance before using infliximab.
  - Once improving, gradually taper steroids (28 days of taper) and consider prophylactic antibiotics, antifungals and anti PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
  - Report event to DSSM.
- *Grade 3 or 4*:
  *Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 diarrhea: life threatening consequences. Grade 3 colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated.*
  - Permanently discontinue study therapy for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study therapy can be resumed after completion of steroid taper.
  - Discontinue study therapy for Grade 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.
  - Report event to DSSM.
  - 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 5 mg/kg once every 2 weeks).
  - Caution: Ensure GI consult to rule out bowel perforation and, if administered, refer to infliximab label for general guidance before using infliximab.
  - Once improving, gradually taper steroids (28 days of taper) and consider prophylactic antibiotics, antifungals and anti PJP treatment (refer to current

NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).

8.5.5 ***Hepatitis/hepatotoxicity***

*(Elevation in AST, ALT, ALP and total bilirubin)*

Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin (TB). Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications). **Infliximab should not be used for management of immune-related hepatitis.** Prompt treatment with steroids is important per guidelines below. For study treatment dose management related to imAEs, see Section 8.5.1 and Table 7.

- *Grade 1 AST or ALT and/or TB elevation*:
  - Continue LFT monitoring per protocol.
- *Grade 2 AST or ALT and/ or TB elevation*:
  *Note:* For patients with metastatic liver disease who enter the study with Grade 2 transaminases, maintain dose and continue study therapy without holding. Otherwise Hold study therapy.
  - Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations are improving or resolved.
  - If no resolution to ≤ Grade 1 (*or baseline*) in 1-2 days, discuss with study physician. If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2 mg/kg/day PO or IV equivalent.
  - If still no improvement within 3-5 days despite prednisone 1-2mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started.
  - If still no improvement within 3-5 days despite 2-4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil). Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
  - Once improving, gradually taper steroids (28 days of taper) and consider prophylactic antibiotics, antifungals and anti PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
  - Report event to DSSM.

*Grade 3 or 4 AST or ALT and/or TB elevation*:

*.For Grade 3:*

- For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN:
- Hold study therapy dose until resolution to Grade ≤1 or baseline.
- Resume study therapy if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper.
- Permanently discontinue study therapy 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 therapy.
- Permanently discontinue study therapy for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.

*Grade 4*

- Discontinue study therapy.

*Grade 3 or 4:*

- 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 with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate mofetil is not available.
  **Infliximab should NOT be used.**
- Obtain a Hepatology consult, abdominal workup, and imaging as appropriate.
- Once improving, gradually taper steroids (28 days of taper) and consider prophylactic antibiotics, antifungals and anti PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
- Report event to DSSM.

8.5.6 ***Nephritis***

*(serum creatinine elevation)*

Obtain a Nephrology consult. 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.). Prompt treatment with steroids is important and 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. For study treatment dose management related to imAEs, see Section 8.5.1 and Table 7.

- *Grade 1*:
  - Monitor serum creatinine weekly and any accompanying symptom.
  - If creatinine returns to baseline, resume its regular monitoring per study protocol.
  - Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.
- *Grade 2*:
  - Hold study therapy until resolution to Grade ≤1 or baseline.
  - Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.
  - Carefully monitor serum creatinine every 2-3 days and as clinically warranted.
  - Consult Nephrology 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 PO or IV equivalent.
  - If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4 mg/kg/day started.
  - Once improving gradually taper steroids (28 days of taper) and consider prophylactic antibiotics, antifungals and anti PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).

- When event returns to baseline, resume durvalumab (and tremelimumab if applicable) at the next scheduled study dose and routine serum creatinine monitoring per study protocol (see Table 2).
- Report event to DSSM.

- *Grade 3 or 4*:
  - Discontinue study therapy.
  - Carefully monitor serum creatinine on daily basis.
  - Consult Nephrology 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 3-5 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 2-4mg/kg/day started.
  - Once improving, gradually taper steroids (28 days of taper) and consider prophylactic antibiotics, antifungals and anti PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation].
  - Report event to DSSM.

### 8.5.7 ***Dermatitis/rash***

Monitor for signs and symptoms of dermatitis (rash and pruritus). Prompt treatment with steroids (topical or systemic based on severity) is important per management guidelines below.

Note: ***If there is any bullous formation of any grade, report event to DSSM immediately and discontinue study therapy.***

For study treatment dose management related to imAEs, see Section 8.5.1 and Table 7.

- *Grade 1*:
  - Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
- *Grade 2*:
  - Hold study therapy.
  - Consider Dermatology consult.
  - Consider symptomatic treatment including oral antipruritics. (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
  - Consider moderate-strength topical steroid.
  - If no improvement of rash/skin lesions occurs within 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent.
  - Consider skin biopsy if persistent for >1-2 weeks or recurs.
  - Report event to DSSM.
- *Grade 3 or 4*:

  For Grade 3, hold study therapy until resolution to Grade ≤1 or baseline.
  - If temporarily holding the study therapy does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 28 days, then permanently discontinue study therapy, see Table 7.
  - For Grade 4, discontinue study therapy.
  - Obtain a Dermatology consult.

- Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent.
- Consider hospitalization.
- Monitor extent of rash [Rule of Nines].
- Recommend skin biopsy (preferably more than 1) as clinically feasible.
- Once improving, gradually taper steroids (28 days of taper) and consider prophylactic antibiotics, antifungals and anti PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
- Report event to DSSM.

### 8.5.8 *Endocrinopathy*

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. Consult Endocrinology as medically indicated. Patients should be evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infection, etc.). For study treatment dose management related to imAEs, see Section 8.5.1 and Table 7.

- Monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine labs depending on suspected endocrinopathy (e.g., blood glucose and ketone levels, HgA1c). Prompt initiation of hormone replacement is important for hypothyroidism.
- For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation (Weber 2012, Di Giacomo 2010).
- If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
- 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 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 x LLN, or TSH >2 x ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider endocrinology consult.
- *Grade 2*: *(including those with symptomatic endocrinopathy)*

  For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study therapy dose until patient is clinically stable. If toxicity worsens, then treat as Grade 3 or Grade 4. Study therapy can be resumed once event stabilizes and after completion of steroid taper. See Table 7.
  - Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan.

- 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 PO or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones).
- *Isolated hypothyroidism* may be treated with replacement therapy without treatment interruption and without corticosteroids.
- *Patients with T1DM* may be treated with appropriate diabetic therapy, without study therapy interruption, and without corticosteroids.
- Once improving, gradually taper steroids (28 days of taper) and consider prophylactic antibiotics, antifungals and anti PJP treatment (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.
- Report event to DSSM.

- *Grade 3 or 4*:

  For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study therapy dose until endocrinopathy symptom(s) are controlled. Study therapy can be resumed once event stabilizes and after completion of steroid taper.

  Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study therapy on the following conditions: a) the event stabilizes and is controlled; b) the patient is clinically stable as per investigator or treating physician's clinical judgement; c) doses of prednisone are ≤10 mg/day or equivalent.

  - Consult Endocrinology 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, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement(e.g., hydrocortisone, sex hormones).
  - For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity.
  - Isolated hypothyroidism may be treated with replacement therapy, without study therapy interruption, and without corticosteroids.
  - Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study therapy interruption, and without corticosteroids.
  - Once improving, gradually taper immunosuppressive steroids (28 days of taper) and consider prophylactic antibiotics, antifungals and anti PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
  - Report event to DSSM.

8.5.9 ***Neurotoxicity***

*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) inclusive of neurology consult as indicated.
  - Perform symptomatic treatment with neurological consult as appropriate.
  - For study treatment dose management related to imAEs, see Section 8.5.1 and Table 7.
- *Grade 2*:
  - Report event to DSSM.
  - 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 PO or IV equivalent.
  - If no improvement within 3-5 days despite prednisone 1-2mg/kg/day PO or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG).
- *Grade 3*:

  Hold study therapy dose until resolution to Grade ≤1. Permanently discontinue study therapy if Grade 3 imAE does not resolve to Grade ≤1 within 28 days.
  - Report event to DSSM.
  - Obtain Neurology consultation.
  - 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 (28 days of taper) and consider prophylactic antibiotics, antifungals and anti PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). Permanently discontinue study therapy if Grade 3 imAE does not resolve within 28 days.
- *Grade 4*:
  - Discontinue study therapy.
  - Report event to DSSM.
  - Obtain Neurology consultation.
  - Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day PO 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 (28 days of taper) and consider prophylactic antibiotics, antifungals and anti PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).

8.5.10 ***Peripheral neuromotor syndromes***
*(Immune-mediated peripheral neuromotor syndromes such as Guillain-Barre and Myasthenia Gravis)*

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.

Patients should be monitored for signs and symptoms that may include peripheral sensory neuropathy, muscle weakness, peripheral neuropathy (including numbness, tingling, and sensitivity to touch). 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. **If Myasthenia Gravis or Guillain-Barre is confirmed, discontinue study therapy.**

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.

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. See Table 7.

- *Grade 1*:
  - Hold study therapy.
  - Contact DSSM.
  - 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. If Myasthenia Gravis or Guillain-Barre is confirmed, discontinue study therapy and report event to DSSM.
- *Grades 2, 3 and 4*:
  - Hold study therapy during work-up of symptoms. If Myasthenia Gravis or Guillain-Barre is confirmed, discontinue study therapy. If negative hold therapy until ≤ Grade 1 and prednisone dose is ≤ 10 mg/day or the equivalent.
  - Report event to DSSM.
  - 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:*

- 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 IVIG and followed by plasmapheresis if not responsive to IVIG.

- *Grade 3*:
  - Hold study therapy dose until resolution to Grade ≤1.
  - Discontinue study therapy if Grade 3 imAE does not resolve to ≤ Grade 1 in 28 days.
  - Recommend hospitalization.
  - Obtain Neurology consult.
  - Report event to DSSM.
- *Grade 4*:
  - Discontinue study therapy.
  - Report event to DSSM.

### 8.5.11 ***Hematologic effect***

Tremelimumab can suppress bone marrow function with myelosuppression as the dose-limiting toxicity. Monitor complete blood cell counts including platelet counts.

- Patients must not begin a new cycle of treatment unless the absolute neutrophil count (ANC) is ≥ 1500 cells/mm$^3$ and platelet count is ≥ *75,000*/mm$^3$. Follow study therapy management and dose modifications as instructed in Table 6 and Table 7.

Patients with previous history of bleeding and/or who are taking anticoagulant medication may have a higher risk of subsequent bleeding; special attention to monitoring these patients in the context of possible bleeding is warranted (Durvalumab IB 2018).

### 8.5.12 ***Myocarditis***

The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. 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). See Table 7. Patients with pre-existing cardiac disorders should be closely monitored for deterioration in their cardiac condition, which could suggest new onset myocarditis. For all grades contact DSSM.

- *For Grade 1 (no definitive findings)*
  - Monitor and closely follow up in 2 to 4 days for clinical symptoms.
  - Obtain cardiology consult.
  - Institute full cardiac work-up (including exclusion of other alternate causes such as infection).
  - Institute appropriate cardiac management.
  - Consider using steroids
- 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]).

### 8.5.13 ***Myositis/polymyositis***

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. Contact DSSM.

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). See Table 7.

- *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.
- *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]).
- *For Grade 4*
  - Discontinue study therapy.
  - 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]).

See Section 8.5.1 and Table 7.

## 8.6 Management of radiation toxicity

### 8.6.1 *Radiation pneumonitis*

Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. Any patient suspected of having radiation pneumonitis should be evaluated immediately by a treating investigator. Radiation pneumonitis may present with fatigue, fever, shortness of breath, nonproductive cough, and a pulmonary infiltrate on chest x-ray.

An effort also must be made to distinguish symptoms of radiation pneumonitis from those of an immune-related event possibly related to durvalumab and tremelimumab (Section 8.5 and Table 7). Pneumonitis has been observed as a toxicity associated with multiple agents blocking the PD-1/PD-L1 pathway, occurring at a frequency between 1% and 5%, and generally low grade when caught early and treated with either withholding of the agent and/or a course of steroid immunosuppression.

Given that delayed radiation toxicities may be at least in part immunologically mediated, it is possible that adding three doses of SBRT to durvalumab/tremelimumab may exacerbate the severity and/or the frequency of these events. It may therefore not be straightforward to attribute such events exclusively to durvalumab/tremelimumab or to radiation, and such events may need to be attributed to the combination.

The infiltrate on chest x-ray should include the area treated to high dose, but may extend outside of these regions. The infiltrates may be characteristically "geometric" corresponding to the radiation portal, but may also be ill defined.

Mild radiation pneumonitis may be treated with nonsteroidal anti-inflammatory agents. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet. Infections should be treated with antibiotics.

### 8.6.2 *Radiation induced liver toxicity*

It is expected that a proportion of patients treated for right lower lobe lung or liver lesions will have transient elevation of liver enzymes following treatment. If up to Grade 3 elevation of liver enzymes is observed, more frequent measurements (at least twice weekly) of the liver enzymes are recommended until the enzymes stabilize or return to baseline levels. Repeat of blood work for all Grade 4 elevations is required at least 5 days following the first abnormal lab value to determine if the Grade 4 levels are transient (defined as lasting < 5 days) or persistent.

Radiation-induced liver disease (RILD) is a clinical syndrome of anicteric ascites, hepatomegaly and elevation of alkaline phosphatase relative to other transaminases that may occur 2 weeks to 3 months following radiation to the liver (Guha 2011). An increase in ALP must be at least 2-fold above the baseline alkaline phosphatase. RILD is unlikely to occur after a mean liver dose of approximately 30 Gy in conventional fractionation. By maintaining a low mean liver dose and sparing a "critical volume" of liver from radiation, stereotactic delivery techniques allow for the safe administration of higher tumor doses. Patients with pre-existing liver disease (e.g., Child-Pugh score of B or C) are at an increased risk (Guha 2011). Treatment of RILD with repeat paracenteses, diuretics, and close follow-up is recommended (Guha 2011). See Table 7 for specific study therapy dose modification instructions.

## 8.7 Liver dysfunction (Hy's Law)

Hy's Law is based on the observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. A diagnosis of potential drug-induced liver injury caused by a study drug can only be determined/inferred by excluding other potential causes of liver injury (e.g., other drugs or viral hepatitis) and by ruling out an obstructive cause for the elevated bilirubin (e.g., alkaline phosphatase should not be substantially elevated) (FDA 2009; Temple 2006).

### 8.7.1 *Definition of cases potentially meeting Hy's Law criteria*

Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- *Patients with AST or ALT baseline values within the normal range* who subsequently present with AST or ALT > 3 times the ULN concurrent with a total bilirubin > 2 times the ULN with no evidence of hemolysis and an alkaline phosphatase < 2 times the ULN or not available.
- *Patients with pre-existing AST or ALT baseline values above the normal range* who subsequently present with AST or ALT > 2 times the baseline values and > 3 times the ULN, or ≥ 8 times the ULN (whichever is smaller) concurrent with a total bilirubin of > 2 times the ULN and increased by one ULN over baseline or > 3 times the ULN (whichever is smaller) with no evidence of hemolysis and an alkaline phosphatase < 2 times the ULN or not available.

### 8.7.2 *Evaluation of potential Hy's Law cases*

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR) and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g. biliary tract) may be warranted. The possibility of progressive disease should be considered.

Potential Hy's Law cases should be reported as serious adverse events (see Sections 10.4.2 and 10.7.2).

## 9.0 DRUG INFORMATION

### 9.1 Tremelimumab

#### 9.1.1 *Description*

Tremelimumab is a human IgG2 monoclonal antibody targeting against CTLA-4. Tremelimumab has an overall molecular weight of approximately 149 kDa including oligosaccharides.

#### 9.1.2 *Formulation*

Tremelimumab will be supplied as a 400 mg vial solution for infusion after dilution. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine-hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate and 0.02% (w/v) polysorbate 80; it has a pH of 5.5. The nominal fill volume is 20 mL. Tremelimumab must be used within the individually assigned expiry date on the label.

#### 9.1.3 *Toxicity*

Refer to the current tremelimumab IB for toxicity information.

#### 9.1.4 *Preparation*

The dose of tremelimumab for administration must be prepared using aseptic technique. Total time from needle puncture of the tremelimumab vial to the start of administration should not exceed 24 hours at 2°C to 8°C (36°F to 46°F) or 4 hours at room temperature. If total time exceeds these limits, a new dose must be prepared from new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

A dose of tremelimumab (75 mg) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.10 to 10 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. A volume of IV solution equal to the volume of tremelimumab to be added to the IV bag must be removed from the bag prior to the addition of tremelimumab. The required volume of tremelimumab is then added to the IV bag such that final concentration is within 0.10 to 10 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin IV bags have been observed. However, administration set containing cellulose-based filters should not be used with tremelimumab.

***Dose calculation of tremelimumab***

The volume of tremelimumab (in mL) to be added to the IV bag is calculated as follows:

- mL = Intended Dose (mg) ÷ tremelimumab concentration (nominal: 20 mg/mL)
  - Tremelimumab 75 mg dose: 75 mg ÷ 20 mg/mL = 3.8 mL
  - Tremelimumab 40 mg dose: 40 mg÷ 20 mg/mL = 2.0mL
    The corresponding volumes of tremelimumab should be rounded to the nearest tenth of an mL (0.1 mL). See Table 6.

#### 9.1.5 *Administration*

Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration. Tremelimumab diluted in IV bag will be administered

at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein using an IV administration set with a 0.2- or 0.22-µm in-line filter over approximately 60 minutes (+/−5 minutes).

The IV line should be flushed with a volume of IV solution 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.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. In the event that the infusion time exceeds this time limit, a new dose must be prepared from new vials. See Section 7.0, Table 4.

## 9.2 Durvalumab (MEDI4736)

### 9.2.1 *Description*

Durvalumab, a human IgG1 kappa monoclonal antibody directed against PD-L1, contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to C1q and the Fcγ receptors.

### 9.2.2 *Formulation*

Durvalumab will be supplied as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL. Durvalumab must be used within the individually assigned expiry date on the label.

### 9.2.3 *Toxicity*

Refer to the current durvalumab (MEDI4736) IB for toxicity information.

### 9.2.1 *Contraindications*

The use of durvalumab is contraindicated in patients who are pregnant or nursing.

### 9.2.2 *Concomitant medications and other substances*

No formal drug-drug interaction studies have been conducted with durvalumab. There are no known clinically significant interactions of durvalumab with other medicinal products.

### 9.2.3 *Preparation*

The dose of durvalumab for administration must be prepared using aseptic technique. 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) or 4 hours at room temperature. If total time exceeds these limits, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

A dose of durvalumab (1500mg) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose with a final durvalumab 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. A volume of IV solution equal to the volume of durvalumab to be added to the IV bag must be removed from the bag prior to the addition of durvalumab. The required volume of durvalumab is then added to the IV bag such that final concentration is within

1 to 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

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.

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed.

***Dose calculation of durvalumab***

The volume of durvalumab (in mL) to be added to the IV bag is calculated as follows:

- mL = Intended Dose (mg) ÷ durvalumab concentration (nominal: 50 mg/mL)
  - Durvalumab 1500 mg dose: 1500 mg ÷ 50 mg/mL = 30.0 mL
  - Durvalumab 750 mg dose: 750 mg ÷ 50 mg/mL = 15.0 mL.

The corresponding volumes of durvalumab should be rounded to the nearest tenth of an mL (0.1 mL). See Table 5.

#### 9.2.4 *Administration*

Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration. Durvalumab diluted in IV bag will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein using an IV administration set with a 0.2- or 0.22-µm in-line filter over approximately 60 minutes (+/−5 minutes).

The IV line should be flushed with a volume of IV solution (0.9% [w/v] saline) 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.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. In the event that the infusion time exceeds this time limit, a new dose must be prepared from new vials. See Section 7.0, Table 4.

### 9.3 Procurement

Durvalumab and tremelimumab will be supplied free of charge by AstraZeneca and distributed via an external vendor. Durvalumab and tremelimumab must be requested by the principal investigator (or his/her authorized designee) at each participating institution (see Information Resources). The initial supply of Durvalumab and tremelimumab may be requested at the time the first patient signs the FC-9 consent form. Durvalumab and tremelimumab will be shipped directly to the investigator whose sites are participating in FC-9.

### 9.4 Shipping

Vials of durvalumab and tremelimumab are shipped at 2°C to 8°C (36°F to 46°F) by overnight express delivery Monday through Thursday excluding holidays.

### 9.5 Storage requirement and stability

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. While there are currently no specific indicators that Durvalumab is photosensitive it is

recommended that Durvalumab is stored in opaque containers during storage to prevent excessive exposure to light.

### 9.6 Transfer of study therapy

Study therapy (durvalumab and tremelimumab) may not be used outside the scope of FC-9, nor can study therapy be transferred or licensed to any party not participating in this clinical trial.

### 9.7 Destruction of study therapy

At the end of an infusion for an individual patient, any remaining or unused study drug should be destroyed at the site according to the institution's policy for drug destruction. At the completion of the study, all unused study drugs will also be destroyed at the site as per institutional policy for drug destruction after the monitoring review is completed by DSSM.

Maintain appropriate records of the disposal, including dates and quantities.

### 9.8 Drug inventory records

It is the responsibility of the investigator to ensure that a current record of study drug disposition is maintained at each study site where drug is inventoried and disposed.

Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area,
- Amount currently in storage area,
- Label ID number or batch/lot number,
- Dates and initials of person responsible for each study drug inventory entry/movement,
- Amount dispensed and returned for each patient, including unique patient identifiers,
- Amount transferred to another area for dispensing or storage,
- Non-study disposition (e.g., lost, wasted, broken), and
- Amount destroyed.

## 10.0 ADVERSE EVENT REPORTING REQUIREMENTS

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or a serious adverse event (SAE), as provided in this protocol. Routine, adverse events of special interest (AESI), and expedited adverse event report forms and their supporting documentation must be submitted to DSSM according to the instructions in Sections 10.4, 10.7, and 10.8.

### 10.1 Definition of an AE

An AE is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, laboratory findings, or other physiologic observations occurring in a patient participating in FC-9. The event does not need to be causally related to study therapy or other requirements of the FC-9 trial to be considered an AE.

- Examples of an AE include, but are not limited to, the following:
  - Any toxicity related to study therapy.
  - Any clinically significant worsening of a pre-existing condition.
  - An AE occurring from a symptomatic overdose of any study therapy, whether accidental or intentional. Overdose is a dose greater than that specified in the protocol.
  - A symptomatic AE that has been associated with the discontinuation of the use of any of the agents included in the study therapy.
  - An AE occurring during a clinical study that is not related to the study therapy, but is considered by the investigator or sponsor to be related to the study requirements, for example, an AE may be an untoward event related to a medical procedure required by the protocol.
- A laboratory test result should be reported as an AE if it meets any of the following criteria:
  - Accompanied by clinical symptoms.
  - Results in a change in study treatment (e.g., dosage modification, treatment interruption or treatment discontinuation).
  - Results in medical intervention (e.g., potassium supplementation for hypokalemia) or treatment discontinuation.
  - Clinically significant per the investigator.
- Examples of clinical events that should **not** be considered AEs:
  - Medical or surgical procedure (e.g., endoscopy, appendectomy). Note, the condition that leads to the procedure may be an AE, but the procedure itself is not.
  - Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

### 10.2 Definition of adverse events of special interest (AESI)

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 to the sponsor. 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.

AESIs for durvalumab and tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy.

These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. See Section 8.5.

If the Investigator has any questions in regards to an adverse event (AE) being an imAE, the Investigator should promptly contact DSSM. For instructions on reporting AESIs, see Sections 10.4.2 and 10.7.2.

AESIs observed with durvalumab/tremelimumab include:

- Diarrhea/colitis
- Pneumonitis/ILD
- Hepatitis/ increases in transaminases
- Neuromuscular toxicity (i.e. events of Guillain-Barre and Myasthenia Gravis)
- Endocrinopathy (i.e. events of hypophysitis, hypopituitarism, adrenal insufficiency, and hyper- and hypothyroidism, Type I diabetes mellitus)
- Dermatitis/rash
- Nephritis
- Pancreatitis
- Infusion reaction
- Hypersensitivity/anaphylactic reaction.
- Myocarditis
- Myositis/polymyositis

Other inflammatory responses that are rare with a potential immune related etiology are also considered as AESIs and include but are not limited to: pericarditis, sarcoidosis, uveitis, and other events involving the eye, skin, hematological, rheumatological events, vasculitis, non-infectious meningitis, and non-infectious encephalitis. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs. Further information on these risks (e.g. presenting symptoms) can be found in Section 8.5 and the current versions of the durvalumab and tremelimumab Investigator Brochures.

## 10.3 Definition of an SAE

An SAE is any untoward medical occurrence that, at any dose, causes one of the following:

- Results in death.
- Is life-threatening.

  The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization

  Hospitalization is any inpatient admission to a health care facility even if for less than 24 hours. Hospitalization or prolongation of a hospitalization constitutes a criterion for an AE to be serious; however, it is not in itself considered an SAE. In the absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE. For example, the following hospitalizations would not require expedited reporting for an SAE:
  - a hospitalization or prolongation of hospitalization needed for a procedure required by the protocol or as part of another routine procedure; or

- a hospitalization for a pre-existing condition that has not worsened.

- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

  This is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect.

  Also, appropriate medical judgment should be exercised in deciding whether SAE reporting is required in other situations, such as important medical events that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of an SAE. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or development of drug dependency or drug abuse.

## 10.4 Events requiring expedited reporting

All events listed in Sections 10.2, 10.3 and 10.4 must be reported in an expedited manner according to the instructions in Section 10.7.

### 10.4.1 *SAEs*

All events meeting the definition of an SAE (see Section 10.3) require expedited reporting.

### 10.4.2 *Other events requiring expedited reporting*

Other events (such as AESIs ≥ Grade 2) must be recorded, reported, and followed up as indicated for an SAE in an expedited manner. See Section 10.2, 10.3 and 10.7 for reporting procedures. This includes the following events:

- Pregnancy exposure to study therapy. (If a pregnancy is confirmed, use of study therapy must be discontinued immediately. See Section 10.5.)
- Lactation exposure to study therapy.
- Medication errors involving study therapy with or without AE symptoms, including product confusion and potential product confusion. (A medication error is any preventable event that may cause or lead to inappropriate use or harm while the study therapy is in control of the healthcare professional or patient. Examples of reportable medication error include administration of unassigned treatment and administration of expired study therapy.)
- Overdose
  - An overdose is defined as a study patient receiving a dose of durvalumab and/or tremelimumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.
  - Any overdose of a study patient with tremelimumab or durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to DSSM. See Section 10.7. There is currently no specific treatment in the event of an overdose of durvalumab or tremelimumab. The investigator will use clinical judgment to treat any overdose.
- Any death, excluding death due to progression of colon cancer.
- Potential Hy's Law cases (see Sections 8.7 and 10.7.2).

- Adverse events of special interest (AESIs) ≥ Grade 2 (see Section 10.2 and 10.7.2).

10.4.3 ***Clinical laboratory abnormalities***

- Abnormal laboratory findings (e.g., clinical chemistry and hematology) or other abnormal assessments (e.g., x-rays and scans) will be recorded as AEs or SAEs if they meet the definition of an AE or SAE, as defined in Sections 10.1, 10.2, respectively, and if the abnormality meets reporting requirements as described in Section 10.4.
- Special reporting requirements related to Hy's Law: All cases confirmed on repeat testing as meeting one of the criteria described in Section 8.7 with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases regardless of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as serious adverse events (see Section 10.7.2).

10.4.4 ***Disease-related events and/or disease-related outcomes not qualifying as SAEs***

An event that is part of the natural course of colorectal cancer does not need to be reported as an SAE. Progression colorectal cancer will be reported in the appropriate eCRF.

*Note:* Any occurrence of secondary malignancy (leukemia secondary to oncology chemotherapy [AML], myelodysplastic syndrome [MDS]) and/or treatment-related secondary malignancy is to be reported as an SAE.

## 10.5 Pregnancy

- If a patient becomes pregnant while receiving study therapy, discontinue study therapy and notify DSSM (see Information Resources). ***The investigator will record pregnancy information on the Pregnancy Notification Form (eCRF) and submit it as an expedited report (within 24 hours) upon learning of a patient's pregnancy.*** (See separate consent for release of pregnancy outcome information.)
- Information about the use in pregnancy encompasses the entire course of pregnancy and delivery, and perinatal and neonatal outcomes even if there were no abnormal findings. Information on the status of the mother and child will be forwarded to DSSM. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will also be reported.
- Should a female partner become pregnant by a male patient participating in the study, the investigator must be notified immediately. (See separate consent for release of pregnancy **outcome** information.) If the female partner signs consent, the outcome of the pregnancy will be reported.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring in association with pregnancy brought to the investigator's attention after the patient has completed the study and considered by the investigator as possibly related to study therapy, must be reported to the DSSM.

## 10.6 Grading the severity of the AE

The NCI CTCAE v4.0 must be used to determine the grade of the AE. The CTCAE provides descriptive terminology and a grading scale for each AE listed. Information regarding the CTCAE can be found on the CTEP Web site at http://ctep.cancer.gov. If you need further assistance, contact DSSM (see Information Resources).

## 10.7 Expedited reporting instructions

### 10.7.1 *Time period for reporting SAEs and other events requiring expedited reporting*

- All SAEs and other events as noted in Sections 10.3, and 10.4 regardless of relationship to study therapy will be reported in an expedited manner as described in Section 10.7. Reporting SAEs (and other applicable events) regardless of relationship to study therapy begins with the first dose of study therapy and continues until 90 days after the last dose of study therapy.
- Any SAE assessed as related to study participation (e.g., protocol-mandated procedures) will be recorded from the time a patient consents to participate in the study up to and including any follow-up contact.
- Following the AE assessment 90 days after the last dose of study therapy, only SAEs determined to be related to study therapy will be reported in an expedited manner using FC-9 Form SAER.
- The investigator must follow up on all SAEs until the events have subsided, until values have returned to baseline, or until the condition has stabilized.

### 10.7.2 *Reporting instructions*

- All SAEs and other events requiring expedited reporting (e.g., AESIs ≥ Grade 2) must be reported using FC-9 Form SAER (eCRF) and submitted to DSSM within 24 hours of the study site personnel's initial notification of the event.
- When reporting potential Hy's Law cases, Form SAER should include the following:
  - Seriousness Criteria = Important Medical Event
  - Assessments and narrative: Include the term "Potential Hy's Law case" in the narrative; the text should also detail what additional study results are available at the time of reporting and what other studies are planned or results pending to further investigate alternative causes of the abnormal ALT/AST or bilirubin that triggered the report. The timing of planned patient follow-up should also be noted.
- NSABP will forward expedited report forms that meet reporting requirements to the FDA and to Astra Zeneca/MedImmune Pharmacovigilance.
- Investigators are responsible for reporting AEs that meet specific criteria to their local IRBs.

## 10.8 Time period and frequency for routine reporting of AEs

- Patients will be monitored for the occurrence of AEs at each scheduled assessment and during any contact with the patient during the study.
- All AEs, including SAEs and other AEs that have been reported on FC-9 Form SAER, regardless of relationship to study therapy, will be recorded on Form AE of the CRF from the first dose of study therapy until 90 days after the last dose of study therapy.

- If the patient stops study therapy and begins a new treatment, AE assessments should be collected *only* up to the date the new therapy begins.
- For routine reporting, **all ≥ Grade 1 AEs** will be reported on Form AE of the CRF.
- The investigator must follow up on all AEs until the events have subsided, until values have returned to baseline, or until the condition has stabilized.
- Following the AE assessment 90 days after the last dose of study therapy, routine reporting is no longer required. (See Section 10.4 for expedited reporting requirements.)

## 10.9 Documentation requested following death

For deaths that occur within 30 days of the last dose of study therapy:

- Autopsy reports should be secured whenever possible and should be submitted to DSSM.
- A copy of the death certificate should be forwarded to DSSM if it is readily available or if it contains important cause-of-death information that is not documented elsewhere.
- Submit the last clinic/office note made before the death or the investigator's note summarizing events resulting in death.

## 11.0 ASSESSMENT OF EFFECT

Response to study treatment in this patient population will follow standard RECIST criteria except in the documentation of progressive disease (PD). In this protocol, patients with progressive radiographic metastatic disease who are clinically asymptomatic and without other significant reason to discontinue therapy (i.e., toxicity, physician's judgement or patient's decision to stop therapy) may continue to receive study therapy per protocol until the next scheduled tumor assessment (Table 2) to confirm progression. If progression is confirmed the date of progression will be at the time of the initial scan indicating progression.

### 11.1 Definitions of measurable and non-measurable disease

#### 11.1.1 *Measurable disease:*

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (PET/CT, CT scan, or MRI) or as ≥ 10 mm with spiral CT scan with 5 mm cuts. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). The same method (CT, MRI, or PET/CT) used at baseline should be used at all other tumor measurement time points.

#### 11.1.2 *Non-measurable disease*

All other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan with 5 mm cuts) are considered to be non-measurable disease.

#### 11.1.3 *Target lesions*

Up to a maximum of five measurable lesions should be identified as target lesions and recorded and measured at baseline. Target lesions (maximum 2 lesions per organ) should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements by CT scan or MRI. 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.

#### 11.1.4 *Non-target lesions*

All sites of disease which are not used as target lesions should be identified as non-target lesions. Location of individual lesions within the liver does not have to be specifically recorded. All sites of non-target lesions must be assessed along with the target lesions.

### 11.2 Response criteria

#### 11.2.1 *Evaluation of target lesions*

- *Complete response (CR)*
  Disappearance of all target lesions
- *Partial response (PR)*
  At least a 30% decrease in the sum of the of LD of target lesions, taking as reference the baseline sum LD

- *Progressive disease (PD)*

  At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since baseline or the appearance of one or more new lesions

- *Stable disease (SD)*

  Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since baseline

11.2.2 ***Evaluation of non-target lesions***

- *Complete response (CR):* disappearance of all non-target lesions,
- *Incomplete response/stable disease (SD)*: persistence of one or more non-target lesion(s).
- *Progressive disease (PD)*: Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

11.2.3 ***Evaluation of best overall response***

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

*Refer to Table 8 for a summary of the criteria that contribute to the determination of response.*

Table 8. Determination of response

| ***Target Lesions*** | **Non-Target Lesions** | **New Lesions** | **Overall Response** |
|---|---|---|---|
| *CR* | CR | No | CR |
| *CR* | Incomplete response/SD | No | PR |
| *PR* | Non-PD | No | PR |
| *SD* | Non-PD | No | SD |
| *PD* | Any | Yes or No | PD* |
| *Any* | PD | Yes or No | PD* |
| *Any* | Any | Yes | PD* |
| *Confirmation of PD in a patient with new lesion(s) or suspected tumor flare is required as outlines in Sections 11.2.1 and 11.2.2. | | | |

## 11.3 Symptomatic deterioration

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." This is also true for "symptomatic deterioration" after therapy is completed. Every effort should be made to document objective progression even after discontinuation of treatment.

## 12.0 PATIENT ENTRY PROCEDURES

### 12.1 Patient consent form

Before study entry, the consent form including any addenda, must be signed and dated by the patient and the person obtaining informed consent. **In addition, before study entry, a copy of the signed and dated consent form must be forwarded to DSSM. All patient signatures (except initials of first, middle, and last names) should be expunged prior to submission.**

### 12.2 Study entry

DSSM will verify that the research site has current IRB approval for the study. Entry will not take place if the IRB approval is not current with IRB oversight responsibility.

All patients must be enrolled through DSSM. Once the entry eCRFs have begun to be entered, submit copies of the redacted signed consent form, and supporting documents to [redacted]

The entry material must be received by DSSM **no later than 4:00 p.m. Eastern Time, Monday through Friday, excluding holidays**. Once received the review process will begin. When the review is complete and approved, an enrollment confirmation will be sent. **This process could involve some unavoidable delays. Therefore, it is necessary to plan adequate time (at least 24 hours) between study entry and the initiation of the patient's study therapy.**

### 12.3 Patient study number and treatment assignment

After all the entry materials have been reviewed and approved, the institution will receive the following via e-mail:

- confirmation of registration and study entry;
- Patient Identification number.

### 12.4 Investigator-initiated discontinuation of study therapy

In addition to the conditions outlined in the protocol, the investigator may require a patient to discontinue study therapy if one of the following occurs:

- the patient develops a serious side effect that cannot be tolerated or that cannot be controlled with other medications,
- the patient's health gets worse,
- the patient is unable to meet the study requirements, or
- new information about the study drugs or other treatments for colon cancer becomes available.

If study therapy is stopped, study data and other materials should be submitted according to the study schedule unless the patient withdraws consent from the study or until there is a diagnosis of a secondary malignancy.

### 12.5 Patient-initiated discontinuation of study therapy

Even after a patient agrees to take part in this study, the patient may stop study therapy at any time. If study therapy is stopped, no new therapy begins and the patient still allows the study doctor to submit information, study data and other materials should be submitted according to the study schedule (Table 2).

## 12.6 **Patient-initiated withdrawal from the study**

If a patient chooses to have no further interaction regarding the study, the investigator must provide DSSM with written documentation of the patient's decision to fully withdraw from the study. Any data collected up to the time of withdrawal from the study will continue to be used.

## 13.0 DATA HANDLING AND RECORDKEEPING

Refer to the "FC-9 eCRF Completion Guidelines" for detailed instructions regarding data collection, AE reporting, and electronic case report form completion.

## 14.0 STATISTICAL CONSIDERATION

### 14.1 Study design

FC-9 is a single arm, study using the combination of durvalumab and tremelimumab for 4 cycles followed by durvalumab as monotherapy cycles 5 through 24 (1 cycle = 28 days). Study therapy will be initiated following 3 doses of palliative hypofractionated radiation on Days −2, −1 and Day 0, prior to beginning Cycle 1.

### 14.2 Statistical design and sample size analysis

The optimal two-stage design (Simon 1989) to test the null hypothesis that $ORR_0 \leq 0.05$ versus the alternative that $ORR_A \geq 0.20$ has an expected sample size of 16.14 and a probability of early termination of 0.54. If the combination study therapy is actually not effective, there is a 0.080 probability of concluding that it is (the target for this value was alpha = 0.10). If the combination study therapy is actually effective, there is a 0.197 probability of concluding that it is not (the target for this value was beta = 0.20).

Patients who complete both Cycle 1 and Cycle 2, and undergo the first restaging scan after Cycle 2 for the determination of tumor response will be determined as evaluable. Non-evaluable patients will be replaced.

After testing the study therapy combination on 12 evaluable patients in the first stage, the trial will be terminated if 0 patients respond. If the trial goes on to the second stage, a total of 21 evaluable patients will be studied. If the total number responding is less than or equal to 2, the combination is rejected. If 3 or more responses are observed (ORR ≥ 14.3%) after the second stage of the study, the combination will be considered for further study.

### 14.3 Monitoring

- A medical review team comprising of the Protocol Chair, NSABP Medical Director, study statistician, designated physician(s), and designated DSSM staff will formally monitor the study on a monthly basis to identify accrual, toxicity, and any endpoint problems that might be developing.
- During the trial, the protocol officer, and designated DSSM staff will participate in a weekly Web-ex with investigators who have a patient enrolled on the FC-9 study. Investigators who have a patient receiving study therapy are required to participate. All FC-9 study staff are encouraged to attend.
- The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns.

## 15.0 PUBLICATION INFORMATION

The publication or citation of study results will be made in accordance with the publication policy of the NSABP that is in effect at the time the information is to be made publicly available.

## 16.0 **REFERENCES**


**Alexandrov 2013**
Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature 2013; 500(7463):415-421.

**Ansell 2015**
Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015; 372(4):311-319.

**Antonia 2015**
Antonia SJ, Goldberg SB, Balmanoukian AS, et al. Phase Ib study of MEDI4736, a programmed cell death ligand-1 (PD-L1) antibody, in combination with tremelimumab, a cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) antibody, in patients (pts) with advanced NSCLC. J Clin Oncol 2015; 33:(suppl; abstr 3014).

**Bezu 2015**
Bezu L, Gomes-de-Silva LC, Dewitte H, et al. Combinatorial strategies for the induction of immunogenic cell death. Front Immunol 2015; 6:187.

**Brahmer 2010**
Brahmer JR, Drake CG, Wollner I, 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):3167-175.

**Brahmer 2012**
Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012; 366(26):2455-2465.

**Chung 2010**
Chung KY, Gore I, Fong L, et al. Phase II study of the anti-cytotoxic T-lymphocyte-associated antigen 4 monoclonal antibody, tremelimumab, in patients with refractory metastatic colorectal cancer. J Clin Oncol 2010; 28(21):3485-3490.

**Demaria 2012**
Demaria S, Formenti SC. Radiation as an immunological adjuvant: current evidence on dose and fractionation. Front Oncol 2012; 2:153.

**Deng 2014**
Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest 2014; 124(2): 687–695.

**Di Giacomo 2010**
Di Giacomo AM, Biagioli M, Maio M. The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications. Semin Oncol. 2010;37(5):499-507.

**Dovedi 2014**
Dovedi SJ, Adlard AL, Lipowska-Bhalla G, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res 2014; 74(19): 5458–5468.

**Durvalumab IB 2018**
Durvalumab (MEDI4736) Investigator Brochure Edition 12.1, AstraZeneca; March 5, 2018.

**Eisenhauer 2009**
Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45(2): 228-247.

**Esposito 2015**
Esposito A, Criscitiello C, Curigliano G. Immune checkpoint inhibitors with radiotherapy and locoregional treatment: synergism and potential clinical implications. Curr Opin Oncol 2015; 27(6):445-451.

**FDA Guidance 2009**
FDA-Guidance. Drug-Induced Liver Injury: Premarketing Clinical Evaluation; July 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf (2009).

**Formenti 2009**
Formenti SC, Demaria S. Systemic effects of local radiotherapy. Lancet Oncol 2009; 10(7):718-726.

**Formenti 2012**
Formenti SC, Demaria S. Radiation therapy to convert the tumor into an in situ vaccine. Int J Radiat Oncol Biol Phy s 2012; 84(4):879-880.

**Formenti 2013**
Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. J Natl Cancer Inst 2013; 105(4):256-265.

**Gaipl 2014**
Gaipl US, Multhoff G, Scheithauer H, et al. Kill and spread the word: Stimulation of antitumor immune responses in the context of radiotherapy. Immunotherapy 2014; 6(5):597-610.

**Galon 2006**
Galon J, Costes A, Sanchez-Cabo F, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006; 313(5795):1960-1964.

**Golden 2012**
Golden EB, Pellicciotta I, Demaria S, et al. The convergence of radiation and immunogenic cell death signaling pathways. Front Oncol 2012; 2:88.

**Guha 2011**
Guha C, Kavanagh BD. Hepatic radiation toxicity: avoidance and amelioration. Semin Radiat Oncol 2011; 21(4):256-263.

**Hamid 2013**
Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med 2013; 369(2):134-144.

**Herbst 2014**
Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014; 515(7528):563-567.

**Ibrahim 2015**
Ibrahim R, Stewart R, Shalabi A. PD-L1 Blockade for Cancer Treatment: MEDI4736. Semin Oncol 2015; 42(3):474-483.

**Klug 2013**
Klug F, Prakash H, Huber PE, et al. Low-dose irradiation programs macrophage differentiation to an iNOS(+)/M1 phenotype that orchestrates effective T cell immunotherapy. Cancer Cell 2013; 24(5):589-602.

**Larkin 2015**
Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015; 373(1):23-34.

**Le 2015**
Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015; 25(372):2509-2520.

**Llosa 2015**
Llosa NJ, Cruise M, Tam A, et al. The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. Cancer Discov 2015; 5(1):43-51.

**MEDI4736 IB**
MEDI4767 (durvalumab) Investigator Brochure 9th Edition, AstraZeneca; January 22, 2016.

**Pages 2005**
Pages F, Berger A, Camus M, et al. Effector memory T cells, early metastasis, and survival in colorectal cancer. N Engl J Med 2005; 353(25):2654-2666.

**Park 2015**
Park SS, Dong H, Liu X, et al. PD-1 restrains radiotherapy-induced abscopal effect. Cancer Immunol Res 2015; 3(25):610–619.

**Pardoll 2012**
Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012; 12(4)12:252-264.

**Patnaik 2012**
Patnaik A, Kang SP, Tolcher AW, et al. Phase I study of MK-3475 (anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. J Clin Oncol 2012; 30(15):(suppl abstr 2512.

**Postow 2012**
Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med 2012; 366(10):925-931.

**Postow 2015**
Postow MA, Callahan MK, Wolchok JD. Immune Checkpoint Blockade in Cancer Therapy. J Clin Oncol 2015; 33(17):1974-1982.

**Rizvi 2015**
Rizvi NA, Hellmann MD, Snyder A, et al. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015; 348(6230): 124-128.

**Sagiv-Barfi 2014**
Sagiv-Barfi I, Rajapaksa A, Czerwinski D, et al. Local tumor irradiation combined with α-PD-L1 immune checkpoint inhibition results in local and systemic anti-tumor responses: Successful translation of a mouse model to a human case series. Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; 2014 Apr 5–9; San Diego, CA. Philadelphia (PA): AACR; Abstract nr 2941.

**Sharabi 2015a**
Sharabi AB, Nirschl CJ, Kochel CM, et al. Stereotactic radiation therapy augments antigen-specific PD-1 mediated anti-tumor immune responses via cross-presentation of tumor antigen. Cancer Immunol Res 2015; 3(4): 345–355.

**Sharabi 2015b**
Sharabi AB, Lim M, DeWeese TL, et al. Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. Lancet Oncol 2015; 16(13):e498-509.

**Siegel 2015**
Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015; 65(1):5-29.

**Simon 1989**
Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989; 10(1):1-10.

**Snyder 2014**
Snyder A, Makarov V, Merghoub T, et al. Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma. N Engl J Med 2014; 371(23):2189-2199.

**Tarhini 2008**
Tarhini AA, Kirkwood JM. Tremelimumab (CP-675,206): a fully human anticytotoxic T lymphocyte-associated antigen 4 monoclonal antibody for treatment of patients with advanced cancers. Expert Opin Biol Ther 2008; 8(10):1583-1593.

**Taube 2014**
Taube JM, Klein A, Brahmer JR, et al. Association of PD-1, PD1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. Clin Cancer Res 2014; 20(19):5064-5074.

**Temple 2006**
Temple, R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Safety 2006; 15(4): 241-243.

**Topalian 2012**
Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012; 366(26):2443-2454.

**Tremelimumab IB**
Tremelimumab Investigator's Brochure; 7th Edition, AstraZeneca; June 7, 2016.

**Tumeh 2014**
Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature 2014; 515(7528):568-571.

**Twyman-Saint Victor 2015**
Twyman-Saint Victor C, Rech AJ, Maity A, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature 2015; 520(7547):373-377.

**Vogelstein 2013**
Vogelstein B, Papadopoulos N, Velculescu VE, et al. Cancer genome landscapes. Science 2013; 339(6127):1546-1558.

**Wang 2014**
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.

**Weber 2012**
Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol. 2012; 30:2691–2697.

**Yadav 2014**
Yadav M, Jhunjhunwala S, Phung QT, et al. Predicting immunogenic tumour mutations by combining mass spectrometry and exome sequencing. Nature 2014; 515(7528):572-576.

**Zitvogel 2010**
Zitvogel L, Kepp O, Kroemer G. Decoding cell death signals in inflammation and immunity. Cell 2010; 140(6):798-804.

## APPENDIX A
## DETERMINATION OF PERFORMANCE STATUS

| ECOG or Zubrod Scale | | Karnofsky Score |
|---|---|---|
| 0 | Fully active; able to carry on all pre-disease performance without restriction | 90–100% |
| 1 | Restricted in physically strenuous activity but ambulatory | 70–80% |
| 2 | Ambulatory and capable of self-care, but unable to carry out any work activities | 50–60% |
| 3 | Capable of only limited self-care; confined to bed or chair more than 50% of waking hours | 30–40% |
| 4 | Completely disabled | 10–20% |

## NCI DEFINITION FOR ACTIVITIES OF DAILY LIVING

Activities of daily living (ADL) are the tasks of everyday life. These activities include:

- eating
- dressing
- getting into or out of bed or chair
- taking a bath or shower
- using the toilet

## APPENDIX B
## HYPOFRACTIONATED RADIATION THERAPY GUIDELINES

The lesion selected for radiation should be a lesion that can be safely radiated with focal irradiation (SBRT) for which radiation at the limited, palliative doses contemplated would be considered medically appropriate and in accord with acceptable radiation oncology practice. Appendix B offers guidance for this study.

### 1.0 Dose Specification

#### 1.1 *Hypofractionated SBRT*

Stereotactic Body Radiation Therapy (SBRT) is the treatment modality utilized for this protocol. Here, stereotactic refers to the targeting, planning, and direction of radiation treatment along any trajectory towards a well-defined and visualized 3-D target. The exact coordinates of this 3D target is what differentiates it from conventional radiation therapy where skin or bony landmarks serve as tumor surrogates. This treatment will require 3-dimensional targeting of the tumor either by fiducial placement or by target visualization using a pre-treatment cone-beam CT (CBCT).

#### 1.2 *Dose fractionation*

All patients will be treated to a single target with a total dose of 27.0 Gy delivered at 9.0 Gy per fraction on three consecutive days with a minimum of 18 hours between treatments required.

#### 1.3 *Target lesion*

A single target lesion identified within the lung or liver will be treated with SBRT as a component of this study. The target lesion should be $\leq 100$ $cm^3$.

#### 1.4 *Premedications*

Analgesic premedication to avoid general discomfort during long treatment duration is recommended when appropriate. Anti-emetics (e.g., Compazine) should be prescribed for those where the 50% isodose line approaches the stomach or bowel. Pretreatment with corticosteroids (e.g., dexamethasone) is not recommended.

### 2.0 Technical Factors

#### 2.1 *Physical factors*

Only 6 mV photons (x-ray) beams produced by a linear accelerator is allowed for this protocol.

#### 2.2 *Treatment platforms*

This trial allows for commercially available photon producing treatment units equipped with a linear accelerator with image (or fiducial) guidance (e.g. Cyberknife, TrueBeam, Trilogy).

### 3.0 Localization, Simulations, and immobilization

#### 3.1 *Patient positioning*

Patients will be positioned in a stable, reproducible position using either a vac bag or thermoplastic mask (lung lesions above the carina) immobilization device. The treatment position should be reproducible from treatment to treatment.

3.2 ***Internal organ motion***

Special considerations must be made to account for the effect of internal organ motion or target positioning and reproducibility. For the purpose of this protocol, accelerator beam gating with the respiratory cycle using the RPM respiratory motion management system is the preferred approach. For those patients treated on the Cyberknife treatment platform, fiducial tracking is also acceptable. Respiratory gating (or tracking) must be reliable enough to insure that the GTV motion is accounted if motion is greater than 0.5 cm.

3.3 ***Localization***

Isocenter localization images should be obtained on the treatment unit immediately before treatment to ensure proper alignment of the simulated fields. These IGRT images can be obtained with planar kV imaging devices. For the Cyberknife system agreement between the treatment unit isocenter or reference point in space must be checked for agreement with the imaging isocenter prior to treatment. For lesions where respiratory gating is utilized, fluoroscopy should be used to confirm the appropriate gating window.

## 4.0 Treatment Planning and Target Volumes

4.1 ***Patient simulation and image acquisition***

Computed tomography is the primary image platform for targeting and treatment planning. The planning CT scans must allow simultaneous view of the patient anatomy and fiducial placement if necessary. Intravenous (I.V) contrast during the planning CT is optional but recommend but can be avoided if a diagnostic CT with contrast was obtained to delineate the tumor and organs at risk within 8 weeks of simulation is available. Image slice thickness should be 1.25 mm per slice.

The target lesion will be outlined by an appropriately trained physician and designated the gross tumor volume (GTV). The target will be drawn using CT with appropriate windowing for the target (lung – pulmonary windows, liver – hepatic windows); however, additional diagnostic images can be fused to assist in target delineation. This includes FDG-PET as well as MRI which is the preferred modality for liver lesions. The target lesion for this study is limited to a GTV volume ≤ 100 $cm^3$.

Planning target volume (PTV) generation will be created following the motion management simulation (i.e., 4D CT). Here, the physician will delineate the primary target and with the assistance of physics support analyze the phases of the respiratory cycle and associated movement in relationship to the tumor in its most superior extent. Respiratory gating should be utilized for tumors with excursion greater than 0.5 cm. A minimum of 0.3-0.5 cm should be added to the movement determined on the motion assessment to generate the PTV.

4.2 ***Dosimetry***

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each dose to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferred. Typically > 10 beams will be used with roughly equal weighting. Generally, more beams are used for larger lesions. When static beams are used, a minimum of 7 non-opposing beams should be used.

For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. In order to obtain acceptable coverage, field aperture size and shape should

correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception should be when observing the minimum field dimension of 3.5 cm when treating small lesions.

As such, prescription lines covering the PTV will typically be the 60-90% line (where the maximum dose is 100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The treatment isocenter or setup point in stereotactic coordinates will be determined from system fiducials (and can be adjusted pre-treatment depending on the results from localization imaging studies) and translated to the treatment record.

***Prescription Dose Constraints for Treatment Planning***

- **Maximum dose**: The treatment plan should be created such that 100% corresponds to the maximum dose delivered to the patient. This point must exist within the PTV.
- **Prescription isodose**: The prescription isodose surface must be > 80% and < 90% of the maximum dose.
- **Prescription Isodose Surface Coverage**: The prescription isodose surface will be chose such that 95% of the PTV is conformally covered by the prescription isodose surface and 99% of the PTV receives a minimum of 90% of the prescription dose.
- **High Dose Spillage**: The cumulative volume of all tissue outside the PTV receiving a dose > 105% of the prescription dose should be no more than 15% of the PTV volume.
- Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose to PTV is ideally < 1.2.

## 5.0 Critical structures

### 5.1 *Pulmonary lesions*

- Skin: A skin contour should be created for all patients. This will be equal to the body contour minus 3 mm. The maximum dose should be less than the prescription dose (i.e., < 27 Gy).
- Lung: Both lungs minus the PTV should be contoured as part of the study. The dose tolerance is below that of the prescription dose. Conformality as described above including conformality index should be achieved.
- Carina and bronchial tree: The distal 2 cm of the trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi should be contoured. The dose to this structure should be less than the prescription dose (i.e. < 27.0 Gy).
- Esophagus: Max dose < 27.0 Gy.

5.2 ***Liver lesions***

- Skin: See above.
- Liver: The entire liver should be contoured. As with the lung, the conformality index should be achieved for target coverage. The GTV should be limited to ≤100 $cm^3$. For the liver $V_{12}$ < 700 cc.
- Stomach or Bowel should be contoured 2 cm above and below the target. The maximum dose should be less than the prescription dose (i.e. < 27 Gy).

## APPENDIX C
## CONTRACEPTION

***Female patient of child-bearing potential***

- Females of childbearing potential are defined as those who are not surgically sterile (i.e., 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).
- 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 9) from the time of screening and must agree to continue using such precautions for 6 months after the last dose of durvalumab and tremelimumab combination therapy and for an additional 3 months 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 patients should also refrain from breastfeeding throughout this period.

***Male patients 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 6 months after receipt of the final dose of durvalumab and tremelimumab combination therapy and for an additional 3 months 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 patients should refrain from sperm donation throughout this period.
- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 9).

***Highly effective methods of contraception***

Highly effective methods of contraception defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are described in Table 9. *Note*: Some contraception methods are **not** considered highly effective (e.g., 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 9. Highly Effective methods of contraception (<1% failure rate)

| Barrier/Intrauterine Methods | Hormonal Methods |
|---|---|
| – Copper T intrauterine device<br>– Levonorgesterel releasing intrauterine system (e.g., Mirena®)[a] | – Etonogestrel implants: e.g., Implanon or Norplant<br>– Intravaginal device: e.g., ethinylestradiol and etonogestrel<br>– Medroxyprogesterone injection: e.g., Depo-Provera<br>– Normal and low dose combined oral contraceptive pill<br>– Norelgestromin/ethinylestradiol transdermal system<br>– Cerazette (desogestrel) |

[a]This is also considered a hormonal method.

Confidential

# Statistical Analysis Plan

| | |
|---|---|
| SPONSOR: | NSABP |
| PROTOCOL TITLE: | A Phase II Study of the Dual Immune Checkpoint Blockade with Durvalumab (MEDI4736) plus Tremelimumab Following Palliative Hypofractionated Radiation in Patients with Microsatellite Stable (MSS) Metastatic Colorectal Cancer Progressing on Chemotherapy |
| STUDY CODE: | NSABP Protocol FC-9 |
| Version | Draft July 06, 2019 |


**For Biostatistics:**

Author: Greg Yothers, PhD, Consulting Statistician

**For Sponsor**:

Reviewer: Alicia Detweiler, Project Data Manager

Approver: Samuel Jacobs, Clinical Research Physician

NSABP Foundation, Inc. Partners In Cancer Research

Confidential

# Table of Contents

# 1. Introduction

This Statistical Analysis Plan (SAP) is written for the clinical trial protocol NSABP FC-9, version dated November 7, 2016. The ICH guideline E3 "Structure and Content of Clinical Study Reports" was used as a guide to the writing of the plan.

# 2. Study Design and Objectives

The FC-9 study is designed as a phase II, open label, single arm study of the dual immune checkpoint blockade with the combination of durvalumab and tremelimumab following hypofractionated palliative radiation in patients with microsatellite stable (MSS) metastatic colorectal cancer (mCRC) who have progressed on chemotherapy.

Study design is a Simon two-stage design (12 patients stage I, 9 patients stage II).

If at least one patient in the first stage have an objective response, the study will proceed to Stage II (*expansion cohort)*. The expansion cohort will enroll 9 additional patients. If ≥ 3 patients have objective response, the study therapy will be considered for further testing.

There will be up to 21 evaluable patients (unevaluable patients will be replaced).

## 2.1 Study Objectives

### 2.1.1 Primary Objective

The primary aim of the study is to estimate the objective response rate (ORR).

### 2.1.2 Secondary Objectives

The secondary objectives of the study will be analyzed separately and are:

- Clinical benefit rate (CBR)
- Duration of Response (DOR)
- Toxicity profile

In addition, exploratory studies will be performed on available data, with the aim:

- Discovering markers that predict treatment benefit

## 2.2 Study Design

### 2.2.1 Stage I futility analysis

If at least one patient in the first stage has an objective response, the study will proceed to Stage II (*expansion cohort)*, otherwise the study will stop for futility.

### 2.2.2 Stage II

If ≥ 3 patients of the combined stage I and II evaluable patients have an objective response, the study therapy will be considered for further testing.

## 2.3 Sample Size Justification

The hypothesis tested to determine the activity of Dual Immune Checkpoint Blockade with Durvalumab plus Tremelimumab expressed in terms of ORR:

H0: ORR <0.05

HA: ORR >0.20

With the specified null and alternative hypotheses, a type I error rate of 0.10 one-sided and power of 0.80 to reject H0 if the true response rate is 20%, a Simon two stage design consists of initially treating 12 evaluable patients. Enrolment should end for an inadequate response (futility) if no patients have an objective response. If at least one patient has an objective response, enrolment continues to a total of 21 patients. If at least 3 responses are seen (ORR > 0.143), the treatment will be considered worth testing further.

# 3. General Analysis Definitions

Data will be analyzed using SAS v 9.4.

Descriptive statistics will be tabulated as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages.
- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, minimum and maximum values.

## 3.1 Study Period and Visit Window Definitions

### 3.1.1 Study Periods

The accrual period is expected to be 24 months.

Enrolled patients will receive the combination of tremelimumab (75 mg IV infusion) and durvalumab (1500 mg IV infusion) on Day 1 for 4 cycles. Beginning with Cycle 5 through Cycle 12, patients will receive durvalumab alone (1500 mg/IV infusion) on Day 1 of each 28 day cycle.

All AEs will be recorded from the first dose of study therapy until 90 days after the last dose of study therapy or at the cessation of study therapy if the patient initiates new anti-cancer therapy, whichever is earlier.

### 3.1.2 Entry, Treatment, and Follow-up

Requirements for study entry and during treatment and follow-up are outlined in section 5 of the protocol.

## 3.2 Planned Analyses

### 3.2.1 Stage I Analysis

The first analysis of ORR will be performed when 1 or more stage I patients have an objective response or 2 years after the last stage I patient is entered, whichever comes first.

#### 3.2.2 Final Analysis

The second and final analysis of ORR will be performed when all patients have completed protocol therapy.

### 3.3 Definition of Analysis Populations

#### 3.3.1 Intent-to-Treat Population (ITT)

The Intent-To-Treat population (ITT) will consist of patients who complete both Cycle 1 and Cycle 2, and undergo the first restaging scan after Cycle 2 for the determination of tumor response will be determined as evaluable. Non-evaluable patients will be replaced.

#### 3.3.2 Safety Population

The Safety population will consist of all patients who receive at least one dose of any study medication.

### 3.4 Calculated Variables

- Study day 1 is defined as the first day any of the study therapy was received.
- The baseline is defined as the last assessment done before or on study day 1.
- Duration of Response (months): (earliest date of censoring, progression, or death – earliest date of response + 1) * 365.25 / 12.
- The cycle start date is the first date of administration of any study drug (with a non-missing dose) by treatment cycle (as reported in the eCRF).
- The visit of premature discontinuation of each drug will be derived from [the date of the last dose reported on the form of discontinuation. This date will be merged with the date of drug administration to determine to which cycle of treatment it corresponds.

### 3.5 Changes to Protocol

No change has been done from the analyses planned in the protocol.

## 4. Study Patients

### 4.1 Disposition of Patients

Table describing number of patients screened, entered, treated, and evaluable.

### 4.2 Protocol Deviations

Protocol deviations will not be analyzed since they are not recorded on the eCRF.

### 4.3 In- and Exclusion Criteria

This will not be analyzed since specific criteria are not collected on the eCRF.

## 5. Demographic and Other Baseline Characteristics

Descriptive statistics with respect to patient characteristics at baseline will be displayed for [the ITT population].

The summary of demographic data and baseline disease characteristics will present the following variables:

- Age, sex, race, and ethnicity
- ECOG performance status (0 to 1)
- Time since initial diagnosis of colon cancer

## 6. Safety Evaluation

The safety analyses will be presented on the [ITT population].

### 6.1 Extent of Exposure

The exposure to each study drug will be summarized in terms of:

- Number of started cycles
- Total cumulative dose

### 6.2 Adverse Events

Frequency and severity of adverse events categorized using the NCI Common Terminology Criteria for Adverse Events version [4.0 (CTCAE v4.0)] will be tabulated. The adverse events are coded using MedDRA Version [18.1]. AE rates will be described by dose level without regard to attribution. Treatment Emergent Adverse events (TEAEs) will be analyzed in terms of their type, incidence and severity. An adverse event is treatment emergent if it occurs on or after the date of the first administration of study drug. According to the protocol, only treatment emergent AEs are collected on this study.

A summary table including the number of AEs and the number of patients with at least one:

- AE
- Grade 1/2 AE
- Grade 3 or 4 AE
- Serious AE
- AE leading to permanent discontinuation of either one of both study treatments
- Fatal AE
- AE leading to death

will be presented.

Tabulations of the number of patients who experienced treatment emergent adverse events as well as grade of the events will be presented by system organ class and preferred term. Patients will only be counted once for each preferred term. In case a patient experienced the same event more than once, the worst grade will be presented.

Listings of all AEs detailing all AE information by patient with flags for SAE, AE leading to treatment discontinuation, Fatal AE, and AE leading to death.

## 6.3 Deaths

The number of deaths will be tabulated together with the primary cause of death. The details of the 'other will be included in the listing.

# 7. Efficacy Analysis

The efficacy analyses will use data from tumor assessments for all subjects at baseline and then after every 2 cycles (8 weeks) of treatment. The overall response to the treatment is classified as Complete Response (CR), Partial Response (PR), Stable Disease (SD) or Progressive Disease (PD) and is recorded in the eCRF at each tumor assessment.

## 7.1 Primary Analysis of Stage II: Objective Response Rate

The ITT population will be used to test the effects of therapy on ORR. The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Confirmation of complete or partial response IS NOT required.

A summary table presenting % of patients with a best overall response of CR, PR, SD and PD will be made. ORR will be calculated as % of patients with CR or PR at any time during the treatment (including unscheduled assessments). The 95 % confidence interval of the ORR proportion will be reported using exact method based on the binomial distribution (Clopper-Pearson method). The denominator will be the number of patients in the ITT population.

The primary objective of the trial will be reached if at least 3 responses are observed among 21 evaluable patients (14.3%).

## 7.2 Secondary Efficacy Analyses

The secondary endpoints will be analyzed with a descriptive intent only. The secondary objectives for stage II of the study will be analyzed separately on the ITT population.

### 7.2.1 Clinical Benefit Rate

CBR is defined as the proportion of patients with no progression or death at 16 weeks.

The 95% confidence interval of the CBR will be reported using exact method based on the binomial distribution (Clopper-Pearson method). The denominator will be the number of patients in the ITT population.

### 7.2.2 Duration of Response

DOR is defined as the time (in months) from best response to progression, censoring, or death) among patients with a response.

The median and a 95 % confidence interval of DOR will be reported using Kaplan-Meier methods.

## 8. Exploratory Translational Studies

Immune markers will be explored by NSABP out of the scope of this SAP.

## 9. Appendices

Appendix 1: List of Statistical Tables

Appendix 2: List of Data Listings

## Appendix 1: List of Statistical Tables

| Table Number | Table Title | Population |
|---|---|---|
| Table 01.01 | Patient Disposition | All enrolled patients |
| Table 01.02 | Completion Status and Discontinuation from study drugs | ITT |
| Table 01.03 | Completion Status and Discontinuation from the Study | ITT |
| | | |
| Table 02.01 | Demographic and Other Baseline Characteristics | ITT |
| | | |
| Table 03.01 | Extent of Exposure | ITT |
| | | |
| Table 04.01 | Summary of Adverse Events | Safety |
| Table 04.02 | Grade 1/2 Adverse Events by SOC and PT | Safety |
| Table 04.03 | Grade 3/4 Treatment-Emergent Adverse Events by SOC, PT | Safety |
| Table 04.04 | Adverse Events Leading to Discontinuation of Study Therapies, by SOC and PT | Safety |
| Table 04.05 | Fatal Adverse Events by SOC and PT | Safety |
| Table 04.06 | AEs leading to Death by SOC and PT | Safety |
| Table 04.07 | Deaths | Safety |
| | | |
| Table 05.01 | Best overall response | ITT |
| Table 05.02 | Objective Response Rate | ITT |
| Table 05.03 | Clinical Benefit Rate at 16 weeks | ITT |
| Table 05.04 | Duration of Response | ITT |
| Figure 05.05 | Kaplan-Meier Duration of Response Plot | ITT |

## Appendix 3: List of Data Listings

| Listing Number | Listing Title | Population |
|---|---|---|
| Listing 01.01 | Patient Disposition | All |
| Listing 01.02 | Patient Completion of Study Treatment and of Study | All |
| Listing 02.01 | Demographic and Other Baseline Characteristics | All |
| Listing 03.01 | Study Drug Administration | All |
| Listing 04.01 | Adverse Events | All |
| Listing 04.02 | Serious Adverse Events | All |
| Listing 04.03 | Fatal Adverse Events | All |
| Listing 04.04 | Deaths | All |
| Listing 05.01 | Tumor response (including ORR and CBR indicators) | All |
| Listing 05.02 | Duration of Response | All |