STU-2021-0171
Randomized Phase II Study of Chemotherapy, Durvalumab and Tremelimumab and Stereotactic Radiotherapy for Advanced Non-Small Cell Lung Cancer

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Study Drug/Treatment: Durvalumab (trade name: Imfinzi) and Tremelimumab

IND/IDE Number: 175817

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Funding Source: AstraZeneca/Medimmune

NCT Number: NCT04786093

Initial version: Version 1.0 – December 1, 2020

Amended: 1.1 – October 24, 2023
2.0 – November 28, 2023

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Amendment/Version # 2.0

PROTOCOL NUMBER- STU-2021-0171
Randomized Phase II Study of Durvalumab and Tremelimumab and Stereotactic Radiotherapy for Advanced Non-Small Cell Lung Cancer

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

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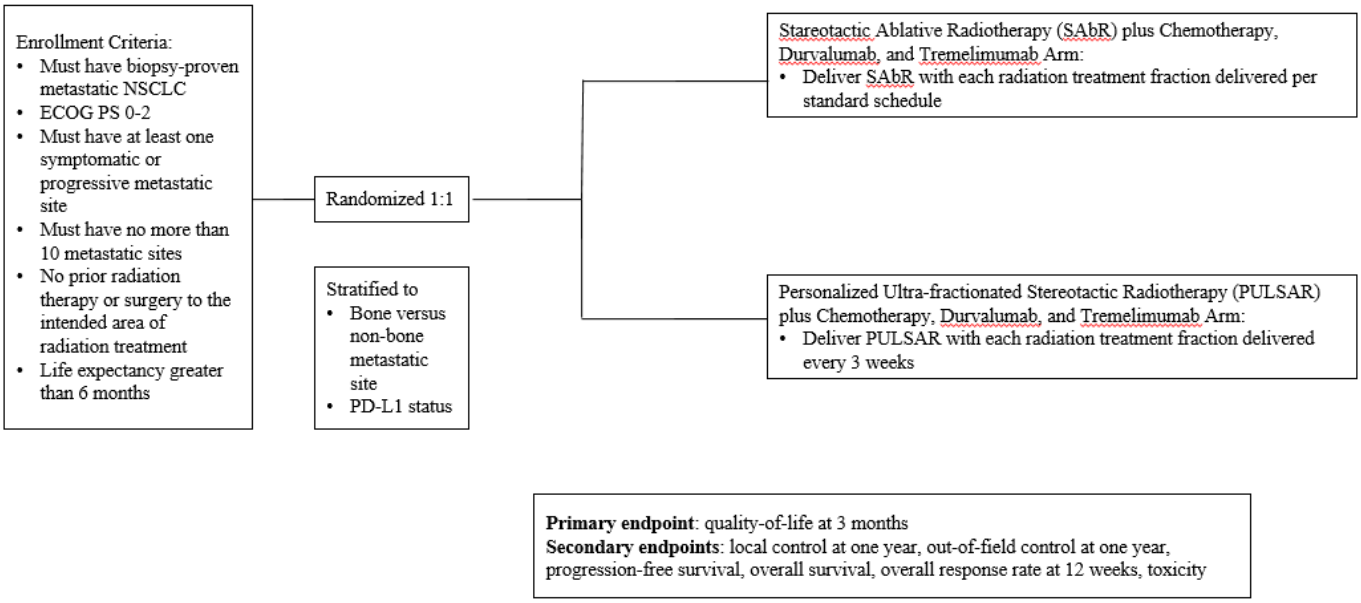
LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOT	Disease Oriented Team
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IDE	Investigational Device Exemption
IHC	Immunohistochemistry
IIT	Investigator-Initiated Trial
IND	Investigational New Drug
IV (or iv)	Intravenously
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
pCR	Pathologic Complete Response
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
p.o.	peros/by mouth/orally
PR	Partial Response
RCB	Residual Cancer Burden
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease

SGOT	Serum Glutamic Oxaloacetic Transaminase
SLD	Sum of the Longest Diameter
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	Randomized Phase II Study of Chemotherapy, Durvalumab and Tremelimumab and Stereotactic Radiotherapy for Advanced Non-Small Cell Lung Cancer
Short Title	Chemoimmunotherapy and Stereotactic Radiotherapy for Advanced NSCLC
Protocol Number	STU-2021-0171
Phase	II
Methodology	Randomized phase II
Study Duration	60 months
Study Center(s)	Single-center
Objectives	To determine the impact of stereotactic radiotherapy and chemotherapy, Durvalumab and Tremelimumab on quality-of-life and oncologic outcomes in patients with advanced non-small cell lung cancer
Number of Subjects	52 patients
Diagnosis and Main Inclusion Criteria	Metastatic non-small cell lung cancer
Study Product(s), Dose, Route, Regimen	Chemotherapy, Durvalumab (Imfinzi) and Tremelimumab and stereotactic radiotherapy, with each fraction of radiotherapy given every other day on a stereotactic ablative radiotherapy (SAbR) schedule or every four weeks on the personalized ultra-fractionated stereotactic adaptive radiotherapy (PULSAR) schedule
Duration of administration	Durvalumab is given for two years or until disease progression or unacceptable toxicity while chemotherapy is given for 4 cycles, and Tremelimumab is given for 5 cycles
Statistical Methodology	The primary endpoint is quality-of-life at 3 months, using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). We assume that a significant improvement in quality of life (QoL) is defined as a rate of ≥ 10% improvement in QoL, which has been shown in validation studies to correlate with "moderate" improvement. Based on prior data of palliative radiotherapy in patients with metastatic cancer, the proportion of historical controls experiencing a positive change of ≥ 10% is 33%. We hypothesize that chemotherapy, Durvalumab and Tremelimumab and stereotactic radiotherapy, in the form of PULSAR and SAbR, will confer a 60% increase in improvement in quality of life over the historical control rate of 33%, for an absolute improvement of 27%. Using a two-sided exact binomial test with a two-sided significance level of 0.1 and 80% power, we estimate that we will need to enroll 23 patients per arm do detect a difference. Accounting for 10% attrition, we will plan to enroll 52 patients.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

It is estimated that 228,820 new cases of lung cancer are diagnosed in the United States in 2020 (Siegel, Miller et al. 2020). Non-small cell lung cancer (NSCLC) encompasses approximately 85% of lung cancer cases in the United States, with the majority of patients presenting with metastatic disease that portends a poor prognosis (Molina, Yang et al. 2008). Classically, the management of patients with metastatic lung cancer with good performance status usually encompasses a platinum-based regimen. In select patients, specific targeted agents can be used if the tumor harbors mutations or gene rearrangements that are targetable, such as *EGFR* mutations or *ALK* rearrangements. More recently, the development of immunotherapy have demonstrated efficacy across several indications for non-small cell lung cancer.

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors (Dunn, Old et al. 2004). PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The PD-1 receptor (CD279) is expressed on the surface of activated T cells (Keir, Butte et al. 2008). It has 2 known ligands: PD-L1 (B7 H1; CD274) and PD-L2 (B7 DC; CD273) (Okazaki and Honjo 2007). The PD-1 and PD-L1/PD-L2 belong to the family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T cell response. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T cell proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PD-L1 is constitutively expressed by B cells, dendritic cells, and macrophages (Qin, Coffey et al. 2016). Importantly, PD-L1 is commonly over expressed on tumor cells or on non-transformed cells in the tumor microenvironment (Pardoll 2012). PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T cells leading to the inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous anti-tumor activity.

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti–PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1–mediated inhibition of antitumor immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti–PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti–PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (Iwai, Ishida et al. 2002, Hirano, Kaneko et al. 2005, Zhang, Su et al. 2008, Okudaira, Hokari et al. 2009, Brahmer 2012, Topalian, Drake et al. 2012) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (Powles, Eder et al. 2014, Rizvi, Hellmann et al. 2015, Segal, Ou et al. 2019). In addition, high mutational burden (e.g., in bladder carcinoma (Alexandrov, Nik-Zainal et al. 2013)) may contribute to the responses seen with immune therapy.

In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells (Fife and Bluestone 2008). Blockade of CTLA-4 binding to CD80/86 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. Therefore, it is expected that treatment with an anti–CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

Preclinical data have now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has promising clinical activity. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies, whilst nivolumab and pembrolizumab, two anti–PD-1 agents, and atezolizumab and avelumab, two anti–PD-L1 agents have been granted approvals by agencies such as the U.S. Food and Drug Administration and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous cell non-small cell lung cancer, and non-squamous cell non-small-cell lung cancer. In addition, there are data from agents in the anti–PD-1/PD-L1 class showing clinical activity in a wide range of tumor types.

Nivolumab, a monoclonal antibody inhibitor of PD-1, improved overall survival in patients, increasing 3-year overall survival rate from 8% to 17% with previously treated squamous (Checkmate-017) and nonsquamous (Checkmate-057) non-small cell lung cancer, compared to docetaxel (Borghaei, Paz-Ares et al. 2015, Brahmer, Reckamp et al. 2015, Vokes, Ready et al. 2018). The survival benefit of nivolumab was complemented with a decreased rate of treatment-related adverse events, compared to docetaxel (Horn, Spigel et al. 2017). More recently, nivolumab, in combination with ipilimumab, an anti-CTLA4 monoclonal antibody, increased 1-year progression-free survival over chemotherapy, from 42.6% to 13.2%, in metastatic or recurrent non-small cell lung cancer with a high tumor mutational burden of ≥ 10 mutations per megabase (Hellmann, Ciuleanu et al. 2018). The objective response rate was 45.3% with combination nivolumab and ipilimumab versus 26.9% with chemotherapy.

Pembrolizumab, an inhibitor of the PD-1 receptor, was compared to investigator's choice of platinum-based chemotherapy in patients with previously untreated advanced non-small cell lung cancer with PD-L1 tumor proportion score of 50% or greater, without EGFR or ALK aberrations, increasing overall survival from 14.2 months with chemotherapy to 30.0 months with pembrolizumab, in KEYNOTE-024 (Reck, Rodriguez-Abreu et al. 2019). Moreover, even with crossover to pembrolizumab in patients assigned to chemotherapy, there was an improvement in the hazard ratio for overall survival of 0.49. KEYNOTE-042 demonstrated the benefit of pembrolizumab in patients with PD-L1 tumor proportion score of 1% or greater, over platinum-based chemotherapy, improving overall survival with a favorable toxicity profile (Mok, Wu et al. 2019). However, in an exploratory analysis, no benefit was observed with pembrolizumab over chemotherapy in patients with tumor proportion score from 1 to 49%. However, for these group of patients, pembrolizumab, cisplatin, and pemetrexed in patients with metastatic nonsquamous non-small cell lung cancer without sensitizing EGFR or ALK mutations, based on the improvement in 1-year overall survival compared to cisplatin/pemetrexed alone, increasing from 49.4% to 69.2% with the addition of pembrolizumab, regardless of PD-L1 expression levels (Gandhi, Rodriguez-Abreu et al. 2018). For patients with previously untreated metastatic squamous non-small cell lung cancer, the addition of pembrolizumab to carboplatin and paclitaxel (or nab-paclitaxel) conferred an overall

survival benefit over placebo, regardless of PD-L1 expression, increasing the median overall survival from 11.3 to 15.9 months (Paz-Ares, Luft et al. 2018). Pembrolizumab also increases overall survival with a favorable benefit-to-risk profile over docetaxel in patients previously treated non-small cell lung cancer with at least 1% PD-L1 expression (Herbst, Baas et al. 2016).

In addition to the targeting of PD-1, PD-L1 inhibitors, such as atezolizumab, has also been developed. In IMpower150, patients with previously untreated metastatic nonsquamous non-small cell lung cancer were randomly assigned to atezolizumab plus carboplatin and paclitaxel, bevacizumab plus carboplatin and paclitaxel, or atezolizumab, bevacizumab, carboplatin and paclitaxel, and showed improvement in progression-free and overall survival with atezolizumab plus bevacizumab plus carboplatin plus paclitaxel over the two comparator arms, regardless of PD-L1 expression or *EGFR* or *ALK* genetic alteration status (Socinski, Jotte et al. 2018). In the OAK trial, atezolizumab also has improved efficacy and safety over docetaxel in previously treated patients with non-small cell lung cancer regardless of PD-L1 expression or histology (Rittmeyer, Barlesi et al. 2017, Fehrenbacher, von Pawel et al. 2018).

More recently, the addition of durvalumab and tremelimumab added to chemotherapy in patients with metastatic non-small cell lung cancer reduced the risk of cancer progression or death by 28%, compared to chemotherapy alone, as demonstrated in the POSEIDON trial. Durvalumab, tremelimumab, and chemotherapy improved progression-free survival with a median progression-free survival of 6.2 months from 4.8 months, with chemotherapy alone. Overall survival was improved with durvalumab and tremelimumab plus chemotherapy, increasing median overall survival to14.0 months from 11.7 months, with chemotherapy alone (p=0.00304) (Johnson, Cho et al. 2021). The safety profile of this combination therapy was consistent with the known profiles of each of the medications, with no new safety signals. In addition, durvalumab plus chemotherapy also demonstrated a statistical improvement in progression-free survival over chemotherapy alone (HR=0.74; 95% CI 0.62-0.89; p=0.00093).

Despite the excitement and development of novel systemic therapies such as immunotherapy, it remains that many patients do not respond to treatment, and most patients will ultimately progress through systemic therapy and succumb to their disease. For example, in KEYNOTE-024, median progression-free survival was improved from 6.0 months to 10.3 months with pembrolizumab, with a concomitant improvement in overall survival. These data indicates that while there is a modest improvement in tumor control, most patients will progress, requiring further therapies.

In patients with advanced non-small cell lung cancer, the role for radiation therapy has evolved over the past two decades. Traditionally, radiation therapy for patients with metastatic cancer has been aimed at palliation of sites of metastatic disease that are causing symptoms such as pain or compromise of a vital organ. Typically, these courses of radiation therapy are short, with the goal of treatment to be fast, inexpensive, and effective. There are several strategies for delivery of palliative radiation therapy, with typical courses ranging from a single fraction to a short, multi-fraction approach (Hartsell, Scott et al. 2005, Faria 2014). Radiation Therapy Oncology Group 9714 study did not show a difference in terms of pain and narcotic relief at 3 months, comparing 8 Gy in one fraction versus 30 Gy in 10 fractions, for patients with painful bone metastases (Hartsell, Scott et al. 2005).

More recently, stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiotherapy (SAbR), have been developed and is a mainstay of treatment for patients with non-small cell lung cancer. In patients with medically inoperable early stage lung cancer, stereotactic body radiation therapy confers a high rate of local tumor control

that is safe with a favorable toxicity profile (Timmerman, Paulus et al. 2010, Timmerman, Hu et al. 2018). Significant developments have also been made in the use of stereotactic body radiation therapy for patients with metastatic disease.

In one randomized phase II trial, patients with non-small cell lung cancer and three or fewer sites received first line systemic therapy were enrolled if they had no evidence of disease progression. The patients were randomized to maintenance therapy alone versus local consolidative therapy, either with (chemo)radiotherapy or surgical resection and found that local consolidative therapy portend an improved median progression-free survival compared to maintenance systemic therapy alone (Gomez, Blumenschein et al. 2016). This improvement in progression-free survival translated into an improvement in overall survival, increasing from 17 months with maintenance therapy alone to 41.2 months with local consolidative therapy (Gomez, Tang et al. 2019).

Our group have also investigated the role of SAbR in oligometastatic non-small cell lung cancer. In our single-arm, phase II study of patients with metastatic non-small cell lung cancer with no more than six sites of extracranial disease who failed early systemic chemotherapy, SAbR was used concurrently with erlotinib, resulting in a favorable progression-free survival of 14.7 months and median overall survival of 20.4 months. Moreover, of the 13 patients who had EGFR mutation status analyzed, none were EGFR mutated suggesting that the benefit came from stereotactic body radiation therapy (Iyengar, Kavanagh et al. 2014). We then conducted a randomized, phase II study of maintenance chemotherapy versus maintenance chemotherapy plus SAbR in patients with non-progressive limited metastatic non-small cell lung cancer after induction chemotherapy (Iyengar, Wardak et al. 2018). Compared to patients who received maintenance chemotherapy alone, consolidative SAbR prior to maintenance chemotherapy resulted in an increase of progression-free survival from 3.5 to 9.7 months. Moreover, a randomized, phase II study of SAbR in patients with oligometastatic cancer of variety of different primaries and controlled primary tumor versus palliative standard of care treatments alone, a study termed SABR-COMET, showed an improvement in overall survival (Palma, Olson et al. 2019, Palma, Olson et al. 2020). Moreover, in this study, there was no detriment in quality of life with the addition of SAbR to systemic therapy, in total score as well as the physical, functional, emotional, or social subscales (Olson, Senan et al. 2019).

The PEMBRO-RT randomized phase II evaluated the use of pembrolizumab plus SBRT for advanced non-small cell lung cancer, demonstrating an improvement in overall response rate at 12 weeks with the addition of SBRT to pembrolizumab, with a subgroup analysis demonstrating that PD-L1 negative tumors had the largest benefit from the addition of SBRT (Theelen, Peulen et al. 2019). In a subsequent pooled analysis of PEMBRO-RT trial with a phase I/II trial from MD Anderson, with 148 patients analyzed, an out-of-field (abscopal) response rate (ARR) was significantly increased with the addition of radiotherapy with pembrolizumab, compared to pembrolizumab alone, which was associated with a significant improvement in median overall survival (Theelen, Chen et al. 2020).

Given the promising results of these recent studies, NRG Oncology LU-002 (Principal Investigator: Puneeth Iyengar, MD, PhD) has recently been activated and currently enrolling to elucidate the role of consolidative SAbR in patients with oligometastatic non-small cell lung cancer and its effect on progression-free and overall survival. These results underscore the changing and evolving role of radiation therapy, not only as a method for palliation but as an important component to significantly improve the outcomes in patients with advanced non-small cell lung cancer.

Stereotactic body radiation therapy has also been prospectively evaluated for patients with non-spine bone metastases. In a single-institution phase II trial that compared single fraction SBRT (12 Gy for ≥ 4-cm lesions or 16 Gy for < 4-cm lesions) versus conventional fractionation with 30 Gy in 10 fractions, SBRT had a higher rate of pain response, compared to conventional fractionation, that persisted out to 9 months, with no detriment to treatment-related toxicities or quality of life measures. Notably, local control rates at 1 and 2 years were higher in patients who received SBRT (Nguyen, Chun et al. 2019). In patients with bone-only oligometastatic breast cancer, SAbR is feasible, well-tolerated, and effective in these patients with a dose of 20 Gy delivered in a single fraction (David, Tan et al. 2020).

Alongside the development of stereotactic body radiation therapy over the past few years, the development of immunotherapeutic agents has revolutionized the care of non-small cell lung cancer. Antibody-based inhibitors such as ipilimumab or tremelimumab, an inhibitor of CTLA-4, and pembrolizumab, an inhibitor of PD-1, have been developed and is approved by the United States Food and Drug Administration for many different types of malignancies such as melanoma, head and neck cancer, and non-small cell lung cancer.

In addition to the development of better therapies, quality of life is an increasingly important consideration as patients are living longer with their cancer. Instruments such as the Karnofsky performance status and Functional Living Index have been utilized early on to estimate quality of life (Ganz, Haskell et al. 1988). Early studies of the role of chemotherapy in patients with metastatic non-small cell lung cancer have demonstrated not only improved survival but also quality of life, suggesting that aggressive treatments that can improve survival is not detrimental to a patient's well-being (Bunn and Kelly 1998).

More comprehensive instruments such as the European Organization for Research and Treatment of Cancer QLQ-C30 have been developed as an integrated, modular approach for the evaluation of quality of life in cancer patients (Aaronson, Ahmedzai et al. 1993). The QLQ-C30 version 3.0 evaluates several different measures including global health status, functioning (physical, role, emotional, cognitive, and social), and symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). This instrument have been used in many studies for both systemic and radiotherapeutic interventions for patients with non-small cell lung cancer.

Traditionally, radiation therapy has been used as means to achieve palliation for symptoms such as pain from a metastatic site, superior vena cava syndrome, or respiratory symptoms from an obstructing tumor, underscoring the essential role of radiation therapy to improve quality of life in patients with metastatic non-small cell lung cancer. In a prospective study of 65 patients with locally advanced and metastatic non-small cell lung cancer receiving palliative radiation therapy, the use of the EORTC QLQ-C30 questionnaire demonstrated improved global quality of life and better palliation of respiratory symptoms (Langendijk, ten Velde et al. 2000). In another prospective study of radiation therapy, global quality of life measured by the EORTC QLQ-C30 was a strong prognostic factor for survival in patients with pathologic node-positive non-small cell lung cancer treated with radiation therapy (Langendijk, Aaronson et al. 2000). Interestingly, the choice of fractionation schemes was not detrimental to quality of life when palliative radiotherapy was used for pain palliation (Sau, Sau et al. 2014). In the definitive setting, Radiation Therapy Oncology Group 0617 phase III study, which showed a detriment in survival with dose escalation in patients with locally advanced non-small cell lung cancer, showed a clinically meaningful decline in quality of life in patients who received 74 Gy

versus those who received 60 Gy (Bradley, Paulus et al. 2015, Movsas, Hu et al. 2016, Bradley, Hu et al. 2020).

This underscores that interventions that improve survival or symptoms are positively correlated to improved quality of life, while interventions that lead to a detriment in survival or symptoms negatively affected quality of life, underscoring the importance of evaluating clinical outcomes with that of patient-reported quality of life.

Because of these great strides in improving outcomes with metastatic non-small cell lung cancer with immunotherapy, there is significant interest and enthusiasm for the synergy between radiation therapy and immunotherapy to improve local and systemic control as well as quality of life. To this end, we propose a randomized phase II study, exploring the synergy between stereotactic radiotherapy and durvalumab, tremelimumab, and/or chemotherapy in patients with advanced non-small cell lung cancer.

1.2 Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities

Durvalumab

Durvalumab (initially developed as MEDI4736) is a human monoclonal antibody of the immunoglobulin (Ig) G1 kappa subclass that inhibits binding of PD-L1 (B7-H1, CD274) to PD-1 (CD279) and CD80 (B7-1). MEDI4736 is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. MEDI4736 contains a triple mutation in the constant domain of the Ig G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma receptors involved in triggering effector function.

Durvalumab demonstrated efficacy in patients with stage III non-small cell lung cancer after the receipt of definitive chemoradiotherapy in the PACIFIC trial. The use of durvalumab as consolidation therapy after definitive chemoradiotherapy conferred a significantly longer progression-free survival compared to placebo, increasing median progression-free survival from 5.6 months to 16.8 months (Antonia, Villegas et al. 2017). The increase in progression-free survival translated into a significantly longer overall survival, compared to placebo, with a hazard ratio for death being 0.68 (Antonia, Villegas et al. 2018). The three-year overall survival with durvalumab was 55.3%, compared to 43.5% in the placebo group (Gray, Villegas et al. 2020). Moreover, the use of durvalumab was not detrimental in patient-reported outcomes, a secondary endpoint of the PACIFIC study (Hui, Ozguroglu et al. 2019). In their prespecified and post-hoc exploratory subgroup analysis, the patient with ≥25% PD-L1 level, hazard ratio 0.50, or ≥1% PD-L1 level, hazard ratio 0.59, garnered a statistically significant benefit with durvalumab consolidation over placebo. The positive influence of consolidative durvalumab immunotherapy with chemoradiotherapy in patients with locally advanced lung cancer provides the motivation and zeal to explore treatment strategies with radiation therapy and durvalumab.

In the metastatic setting, the MYSTIC trial showed that Durvalumab with and without Tremelimumab conferred an overall survival benefit in an exploratory analysis of patients with non-small cell lung cancer with blood tumor mutational burder (bTMB) of greater than or equal to 20 mutations per megabase (Rizvi, Cho et al. 2020).

Rationale for Durvalumab Monotherapy Dose

A durvalumab dose of 20 mg/kg every 4 weeks is supported by in vitro data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors and from a phase I trial performed in Japanese patients with advanced solid tumor (D4190C00002).

Pharmacokinetic/Pharmacodynamic Data

Based on available pharmacokinetic (PK)/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W, durvalumab exhibited non-linear (dose dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q2W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q2W is approximately 17 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab (For further information on immunogenicity, please see the current IB).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W (Fairman, Narwal et al. 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens, as represented by AUCss (4 weeks). Median Cmax,ss is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median Ctrough,ss is expected to be higher with 10 mg/kg Q2W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q2W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models. Given the similar area under the plasma drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q2W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Clinical Data
Refer to the current durvalumab Investigator's Brochure (IB) for a complete summary of clinical information including safety, efficacy and pharmacokinetics at the 20mg/kg Q4W regimen.

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

Similar findings have been reported by others (Ng, Lum et al. 2006, Wang, Zhang et al. 2009, Zhang, Shi et al. 2012, Narwal, Roskos et al. 2013). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang, Zhang et al. 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed

that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in pharmacokinetic/pharmacodynamics parameters (Zhang, Shi et al. 2012).

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

Overall Risks with Immunotherapy

Monoclonal antibodies directed against immune checkpoint proteins, such as programmed cell death ligand 1 (PD-L1) as well as those directed against programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system however, there is the potential for adverse effects on other tissues. Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune mediated effects can occur in nearly any organ system, and are most commonly seen as gastrointestinal AEs such as colitis and diarrhoea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism.

Overall Risks with Durvalumab

Risks with durvalumab include, but are not limited to, diarrhoea/colitis, pneumonitis/interstitial lung disease (ILD), endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, type I diabetes mellitus which may present as diabetic ketoacidosis and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis (including pemphigoid, myocarditis, myositis/polymyositis, immune thrombocytopenia, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (eg, Guillain-Barré syndrome, myasthenia gravis, encephalitis, subcutaneous injection site reaction, psoriasis).

For information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab IB.

In monotherapy clinical studies, adverse effects (AE) (all grades) reported very commonly (≥ 15% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9.4% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6.5 % of patients experienced a severe adverse effect (SAE) that was considered to be related to durvalumab by the study investigator. 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 adverse effects.

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

Tremelimumab

Tremelimumab, a CTLA-4 mAb of the IgG 2 kappa isotype, is an immunomodulatory therapy (IMT) that is being developed by AstraZeneca for use in the treatment of cancer. Tremelimumab is a human IgG2 mAb directed against CTLA-4. CTLA-4 is a critical regulatory signal for T-cell expansion and activation following an immune response, and it serves as a natural braking mechanism that maintains T-cell homeostasis. During T-cell activation, T cells upregulate CTLA-4, which binds to B7 ligands on antigen-presenting cells, sending an inhibitory signal that limits T-cell activation. Tremelimumab blocks the inhibitory signal resulting from CTLA-4 binding to B7, leading to indirect prolongation and enhancement of T-cell activation and expansion. An extensive program of non-clinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anticancer agents to support various cancer indications using different dose schedules. Refer to the tremelimumab IB for a complete summary of non-clinical and clinical information; see Section 5.3 for guidance on management of tremelimumab-related toxicities.

To date, tremelimumab has been given to more than 1500 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of tremelimumab monotherapy are summarized in this Section. A detailed summary tremelimumab exposure data can be found in the current version of the tremelimumab IB.

In clinical subjects, tremelimumab exhibits linear (dose-proportional) PK following IV infusion. The estimate of clearance (CL), volume of distribution at steady state (Vss), and terminal-phase half-life is 0.132 mL/h/kg, 81.2 mL/kg and 22.1 days, respectively. These values are consistent with those of natural IgG2. Risks with tremelimumab monotherapy include, but are not limited to, GI effects (colitis, diarrhea, enterocolitis and intestinal perforation), endocrine disorders (hypo- and hyperthyroidism, hypophysitis and adrenal insufficiency), skin effects (rash, and pruritus), elevations in lipase and amylase and clinical manifestations of pancreatitis, other gastrointestinal events e.g. ulcerative colitis, dehydration, nausea and vomiting; hepatic events including hepatitis, and liver enzyme elevations; pneumonitis and ILD; nervous system events including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and proximal muscle weakness; cytopenias including thrombocytopenia, anemia and neutropenia; infusion-related reactions, anaphylaxis, and allergic reactions; renal events including renal failure, acute kidney injury, nephritis, nephrotic syndrome, autoimmune nephritis and electrolyte abnormalities such as hypokalemia; autoimmune diseases including autoimmune arthritis, Sjogren's syndrome and giant cell temporal arteritis; hyperglycemia and diabetes mellitus; and pyrexia. Further information on the identified and potential risks with tremelimumab please always refer to the current version of the tremelimumab IB.

Using pooled data from monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% of patients) were diarrhea, nausea, fatigue, pruritus, decreased appetite, rash, vomiting, dyspnoea, constipation, cough, pyrexia, abdominal pain, decreased weight, headache, asthenia, and anaemia. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab and approximately 45% of patients experienced an SAE.

A detailed summary of tremelimumab monotherapy AE data can be found in the current version of the tremelimumab IB.

<u>Durvalumab and Tremelimumab Combination Therapy</u>
A population PK model was developed for durvalumab using monotherapy data from the Phase 1 study, CD-ON-MEDI4736-1108 (N = 292; doses of 0.1 to 10 mg/kg Q2W or15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight on PK of durvalumab (coefficient of ≤ 0.5). The impact of body weight-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 weight of ~75 kg). A total of 1000 subjects were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens yield similar median steady-state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen. Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (N = 654; doses of 0.01 to 15 mg/kg Q4W or every 90 days; metastatic melanoma) (Wang, Kang et al. 2014). The population PK model indicated minor impact of body weight on PK of tremelimumab (coefficient of ≤ 0.5). The weight-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body weight of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1,000 subjects with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body weight-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen. Similar findings have been reported by others (Ng, Lum et al. 2006, Wang, Zhang et al. 2009, Narwal, Roskos et al. 2013, Gomez, Blumenschein et al. 2016). Wang and colleagues investigated 12 mAbs and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang, Zhang et al. 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in PK/pharmacodynamics parameters (Gomez, Blumenschein et al. 2016).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on an average body weight of 75 kg, a fixed dose of 750 mg Q2W durvalumab is equivalent to 10 mg/kg Q2W, 1500 mg Q4W durvalumab is equivalent to 20 mg/kg Q4W, and 75 mg Q4W tremelimumab is equivalent to 1 mg/kg Q4W.

The safety of durvalumab + tremelimumab combination therapy was initially evaluated in the ongoing dose escalation and dose expansion Study 006, in patients with NSCLC, and is being studied in a number of other ongoing clinical trials, in a number of different indications, and has to date shown a manageable safety and tolerability profile.
The types of risks with the combination of durvalumab + tremelimumab (based on an equivalent durvalumab dose of 20m/kg and a tremelimumab dose of 1mg/kg) are similar to those for durvalumab and tremelimumab monotherapy. Emerging data from study 006, other studies evaluating the combination, and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these immune-mediated toxicities.

For information on all identified and potential risks with the durvalumab+tremelimumab combination please always refer to the current version of the durvalumab IB.

In durvalumab+tremelimumab combination studies at the dose of durvalumab 20mg/kg and tremelimumab 1mg/kg AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, diarrhea, nausea, dyspnea, decreased appetite, pruritus, vomiting, anaemia, constipation, cough, abdominal pain, pyrexia, back pain, arthralgia, hypothyroidism, asthenia, oedema peripheral, weight, decreased hyponatraemia and rash.

Approximately 15% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately 15% of patients experienced an SAE

that was considered to be related to durvalumab and tremelimumab by the study investigator.

A detailed summary of durvalumab + tremelimumab combination AE data can be found in the current version of the durvalumab IB.

Stereotactic Ablative Radiotherapy (SAbR)
Stereotactic ablative radiotherapy (SAbR) (also known as stereotactic body radiation therapy (SBRT)) is an effective form of radiation therapy that allows for the delivery of high-dose radiation to a target in one or few fractions with a high degree of precision. SAbR allows for the ability to deliver ablative doses of radiation therapy conferring excellent tumor control with the precision, limiting dose to adjacent normal tissue and toxicity.

In patients with advanced non-small cell lung cancer, SAbR appears to be very well tolerated. In the multicenter phase II study evaluating the role of local consolidative therapy in oligometastatic non-small cell lung cancer, 20% (five patients) of the 25 patients enrolled on the local consolidative therapy arm had grade 3 adverse events. Two patients had radiation-induced esophagitis, one had anemia related to irradiation of the spleen, one had pneumonitis from a rib fracture, and one developed right upper quadrant pain that was thought to be related to cholelithiasis [11]. No patients in either arm of the study had a grade 4 adverse event. In the long-term update, there was no additional adverse events [12]. In our randomized study of consolidative radiotherapy for oligometastatic lung cancer, there was no grade 5 events but four of the fourteen patients on the SAbR plus maintenance chemotherapy arm had grade 3 toxicity attributable to SAbR (2 respiratory, 1 infectious, 1 hematologic) [13]. However, in the SABR-COMET trial, there were 4.5% (3 of 66 patients) enrolled on the SAbR treatment group had treatment-related grade 5 events, including radiation pneumonitis, pulmonary abscess, and subdural hemorrhage to repair a radiation-related perforated gastric ulcer [15]. No patients in the control group had a grade 5 event.

1.3 Rationale

Given the recent, promising data on the development of Durvalumab in locally advanced non-small cell lung cancer as well as the development of other immunotherapeutic agents, the use of immunotherapy is becoming more and more common in varying presentations of non-small cell lung cancer. While many of these trials of immunotherapy have shown promise over standard chemotherapy regimens, the response rates to immunotherapy are disappointingly low, ranging from 15-40%.

The data from our group as well as others have demonstrated the efficacy of stereotactic radiotherapy as an effective treatment to achieve local control and is considered a standard of care in patients with metastatic non-small cell lung cancer.

This study will evaluate the impact of chemotherapy, durvalumab, tremelimumab and stereotactic radiotherapy, with patients randomized to two different stereotactic radiotherapy schedules. SAbR is typically delivered in 1 to 5 fractions, with each fraction given consecutively daily or every other day. We will also explore the effects of longer time intervals between stereotactic radiotherapy fractions, which we termed: Personalized Ultra-fractionated Stereotactic Adaptive Radiotherapy or PULSAR. With the PULSAR radiotherapy schedule, each stereotactic radiotherapy fraction will be given once every three weeks.

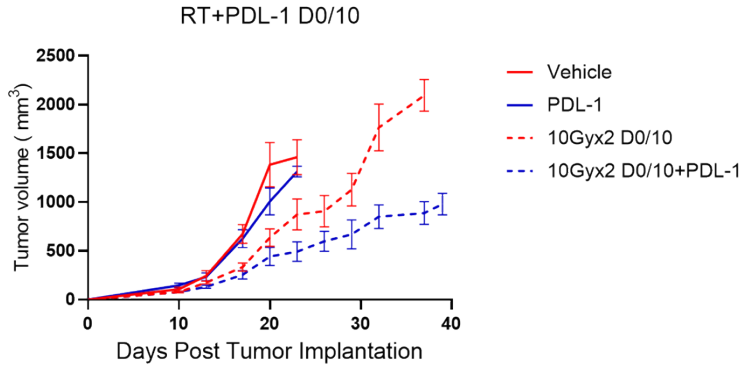
PULSAR sets its premise on delivering radiotherapy over intentionally, longer, infrequent intervals between each radiation treatment, in contrast to historical schedules (i.e. daily fractions) in an effort to activate the immune system and avoid the potentially

immunosuppressive effect from ablative radiotherapy. The interval between each fractions can be irregular, episodic, or triggered, depending on the response profile for each individual patient and can elicit additional tumor kill as well as an *in situ* vaccination booster, which, in combination with systemic immunotherapy, can synergize and improve disease control. Moreover, each radiotherapy fraction can be adapted in real time, depending on changes with the patient and disease status (e.g. anatomy, tumor microenvironment, systemic markers, patient status). Finally, radiotherapy can be continued as needed until the tumor becomes eradicated or becomes a chronic, manageable disease.

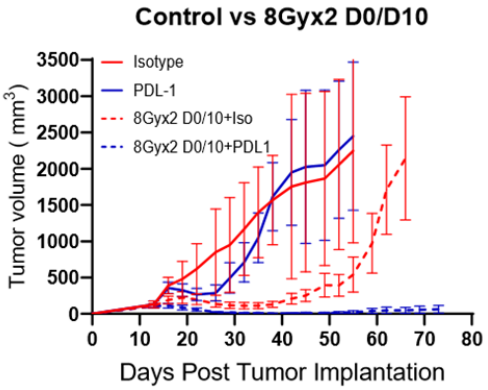
This stereotactic radiotherapy schedule has been supported by preclinical data in murine studies performed by our group. For preclinical evaluation of this strategy, we utilized an orthotopic murine model with immunocompetent C57BL/6 mice and the very aggressive, radioresistent Lewis mouse lung cancer cell line (Moore, Hsu et al. 2021). Four cohorts were created with eight to ten animals were utilized for each cohort. Cohort 1 was mice with no treatment, given vehicle only. Cohort 2 was given a PD-L1 antibody inhibitor. Cohort 3 consisted of mice receiving radiation therapy alone, with each fraction delivered 10 days apart. Cohort 4 comprised of mice receiving radiation therapy, similar to cohort 3, plus the addition of the PD-L1 antibody inhibitor. Radiation therapy was delivered, starting 14 days after the creation of the orthotopic implant with a dose of 10 Gy delivered per fraction. A PD-L1 antibody inhibitor was administered two days prior to delivery of radiation therapy.

Figure 1. Results of tumor growth delay experiment using a split course of radiation therapy with and without a PD-L1 antibody inhibitor in an orthotopic C57BL/6 immunocompetent mouse using Lewis mouse lung carcinoma cells.

Figure 1 illustrates the results of our preclinical studies. We observed that the administration of PD-L1 alone (cohort 2) did not change the tumor growth curve, compared to vehicle alone (cohort 1). When two 10 Gy fractions were delivered with each fraction separated by 10 days (cohort 3), there was a statistically significant delay in tumor growth compared to the PD-L1 antibody only cohort or vehicle only cohort. Interestingly, when radiation therapy, with two fractions given 10 days apart, is delivered in mice receiving the PD-L1 antibody inhibitor, there was a significant reduction in tumor growth, compared to the other three mice cohorts.



Lewis lung carcinoma cells are known to be poorly immunogenic and PD-L1 negative. We performed our preclinical study in MC38 colon cancer cells, which are known to be more immunogenic and express PD-L1 (**Figure 2**). We found that when two doses of radiotherapy (8 Gy) are given 10 days apart, there was a significant delay in tumor growth (red dotted line). When two doses of radiotherapy (8 Gy) given 10 days apart are given in conjunction with a PD-L1 antibody, all of the treated mice had no tumor growth (blue dotted line).



Trial Summary

This randomized phase II study will investigate the role of chemotherapy, durvalumab and tremelimumab, combined with stereotactic radiotherapy in patients with advanced non-small cell lung cancer with progressive or symptomatic metastatic disease. SAbR and PULSAR will provide superior local control of metastatic disease with improved systemic control with the use of chemotherapy, durvalumab and tremelimumab, improving quality of life and cancer outcomes, in patients with advanced and metastatic non-small cell lung cancer.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To assess the impact of chemotherapy, Durvalumab and Tremelimumab and stereotactic radiotherapy, in the form of stereotactic ablative radiotherapy (SAbR) or personalized ultra-fractionated stereotactic adaptive radiotherapy (PULSAR), on improving QoL (quality of life) in patients with metastatic non-small cell lung cancer using the EORTC-QLQ30 instrument

2.2 Secondary Objectives

2.2.1 To evaluate the effect of chemotherapy, Durvalumab and Tremelimumab and PULSAR or SAbR on local control

2.2.2 To assess the effect of chemotherapy, Durvalumab and Tremelimumab and PULSAR or SAbR on out-of-field control (termed abscopal response)

2.2.3 To determine the effect of chemotherapy, Durvalumab and Tremelimumab and PULSAR or SAbR

Figure 2. Results of tumor growth delay experiment using a split course of radiation therapy with and without a PD-L1 antibody inhibitor in an orthotopic murine model using MC38 colon cancer cells.

on progression-free survival

2.2.4 To determine the effect of chemotherapy, Durvalumab and Tremelimumab and PULSAR or SAbR on overall survival

2.2.5 To determine the effect of chemotherapy, Durvalumab and Tremelimumab and PULSAR or SAbR on overall response rate at 12 weeks

2.2.6 To determine the effect of chemotherapy, Durvalumab and Tremelimumab and PULSAR or SAbR on toxicity

2.3 Endpoints

The primary endpoint of this study is quality of life (QoL). The secondary endpoints of this study include local control (LC), out-of-field control, overall response rate (ORR) at 12 weeks, progression-free survival (PFS), overall survival (OS), and toxicity.

3.0 SUBJECT ELIGIBILITY

Eligibility waivers are not recommended; however, if warranted, prior approvals are required per Section 11.5.1. Subjects must meet all inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Once registered, a subject is still required to meet all inclusion and exclusion criteria on the first day of treatment, prior to treatment.

3.1 Inclusion Criteria

3.1.1 Patients must have biopsy- or liquid biopsy-proven metastatic non-small cell lung cancer and eligible for receipt of chemoimmunotherapy, based on standard of care

3.1.2 Patients can present with either *de novo* metastatic disease or recurrent disease

3.1.3 Patients must have at least one (1) symptomatic or progressive metastatic sites with no more than 10 metastatic sites, based on standard imaging studies

3.1.4 Patients cannot have received any prior radiation therapy or surgery to the intended radiation treatment area (index lesion)

3.1.5 Patients with brain metastases may be enrolled if all lesions are treated with radiation therapy or surgery prior to start of protocol therapy

3.1.6 Metastases in major lower extremity weight-bearing bones or spine should undergo surgical stabilization if indicated

3.1.7 Age greater than or equal to 18 years.

3.1.8 Both men and women and members of all races and ethnic groups will be included

3.1.9 Eastern Cooperative Oncology Group Performance status 0 to 2 (**Appendix A**)

3.1.10 Adequate normal organ and bone marrow function as defined by:

- Hemoglobin ≥9.0 g/dL
- Absolute neutrophil count (ANC) ≥ 1.0×10^9 /L
- Platelet count ≥75×10^9/L

- Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
- AST (SGOT)/ALT (SGPT) ≤2.5X institutional upper limit of normal unless liver metastases are present, in which case it must be ≤5X ULN
- Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine CL>40 mL/min by the Cockcroft-Gault formula [67] or by 24-hour urine collection for determination of creatinine clearance:
  - Males:
    - Creatinine CL (mL/min) = $\frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$
  - Females:
    - Creatinine CL (mL/min) = $\frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$

3.1.11 All men, as well as women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for *90* days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

Medically accepted forms of birth control include male condoms plus spermicide, diaphragm, cervical cap, the placement of a Copper T intrauterine device (IUD), birth control pills, Levonorgesterel-releasing intrauterine system (IUS), hormone implants or injections, or combined pill, minipill patch, or a partner who has undergone a vasectomy (surgical sterility).

3.1.11.1 A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.1.12 Life expectancy greater than six (6) months

3.1.13 Body weight greater than 30 kg

3.1.14 Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (e.g., Health Insurance Portability and Accountability Act in the US, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

3.1.15 Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

3.2 Exclusion Criteria

3.2.1 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:

- Patients with vitiligo or alopecia
- Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
- Any chronic skin condition that does not require systemic therapy
- Patients without active disease in the last 5 years may be included but only after consultation with the study physician
- Patients with celiac disease controlled by diet alone

3.2.2 Subjects may not be receiving any other investigational agents for the treatment of the cancer under study.

3.2.3 Patients with untreated brain metastases

3.2.4 Patients with progressive metastatic disease involving the skin or subcutaneous tissues, esophagus, stomach, intestines, or mesenteric lymph nodes that are felt to be too high risk to treat with radiation therapy to protocol dose.

3.2.5 Patients cannot have pathologic fracture at the evaluated site

3.2.6 Patients cannot have untreated spinal cord compression

3.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Durvalumab, Tremelimumab, or other agents used in study

3.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that, in the opinion of the investigator, would limit compliance with study requirements

3.2.9 Subjects must not be pregnant or nursing due to the potential for congenital abnormalities and the potential of this regimen to harm nursing infants

3.2.10 Male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of Durvalumab monotherapy

3.2.11 Participation in another clinical study with an investigational product during the last 3 months

3.2.12 Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study

3.2.13 Receipt of the last dose of anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies) ≤7 days prior to the first dose of study drug If sufficient wash-out time has not occurred due to the schedule or PK properties of an

agent, a longer wash-out period will be required, as agreed by AstraZeneca/MedImmune and the investigator

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

3.2.15 Any concurrent immunotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.

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

3.2.17 History of allogenic organ transplantation

3.2.18 History of another primary malignancy except for:
- Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of immunotherapy and of low potential risk for recurrence
- Adequately treated non-melanoma skin cancer or lentigo malignant without evidence of disease
- Adequately treated carcinoma in situ without evidence of disease

3.2.19 History of leptomeningeal carcinomatosis

3.2.20 History of active primary immunodeficiency

3.2.21 Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HbsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA

3.2.22 Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:
- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

3.2.23 Receipt of live attenuated vaccine within 30 days prior to the first dose of immunotherapy. Other forms of vaccines, such as mRNA, recombinant protein, and non-replicating vector-based vaccines, are permitted. Note: Patients, if

enrolled, should not receive live vaccine whilst receiving immunotherapy and up to 30 days after the last dose of immunotherapy

3.2.24 Receipt of any medication listed in **Section 4.3**

4.0 TREATMENT PLAN

4.1 Chemotherapy and Immunotherapy Dosage and Administration

4.1.1 All systemic chemotherapeutic and immunotherapeutic regimens will be delivered according to standard dosing and administrative routes. Dose adjustments will be made per standard protocol under the care of the treating medical oncologist.

4.1.2 Patients will receive 1 dose of Tremelimumab (75 mg) via IV infusion over 1 hour, which will be followed by Durvalumab (1500 mg) via IV infusion over 1 hour, starting approximately 1 hour (maximum 2 hours) after the end of the Tremelimumab infusion.

Chemotherapy will start approximately 1 hour (maximum 2 hours) after the end of the Durvalumab infusion.

If there is no clinically significant concerns after the first cycle, then at the Investigator's discretion, Durvalumab can be given immediately after Tremelimumab in subsequent cycles.

If there is not clinically significant concerns after the first cycle, reducing the observation period after Durvalumab administration to 30 minutes is recommended, at the Investigator's discretion.

4.1.3 Immunotherapy Regimens, Administrative Routes, and Duration of Therapy

REGIMEN DESCRIPTION				
Agent	**Dose**	**Route**	**Schedule**	**Duration of Therapy**
Durvalumab	1500 mg every 3 weeks for 4 cycles followed by durvalumab monotherapy 1500 mg every 4 weeks	Intravenous over 60 minutes	Day 1	Until disease progression or unacceptable toxicity
Tremelimumab	75 mg every 3 weeks for 5 cycles	Intravenous over 60 minutes	Day 1	Maximum of 5 doses

An additional dose of durvalumab and tremelimumab will be given at week 16 post-chemotherapy. In the case of dose delay(s), more than 1 durvalumab and tremelimumab combination dose can be given at and after week 16 post-chemotherapy to ensure that up to 5 combination doses are administered.

4.1.4 Chemotherapy Regimens, Administrative Routes, and Duration of Therapy

REGIMEN DESCRIPTION				
Agent	**Dose**	**Route**	**Schedule**	**Duration of Therapy**

Carboplatin + Paclitaxel (squamous patients only)	Paclitaxel 200 mg/m^2 Carboplatin AUC 5 or 6	Paclitaxel and Carboplatin both IV infusions	Paclitaxel on Day 1 of each 21-day cycle Carboplatin on Day 1 of each 21-day cycle	4 cycles
Carboplatin + Abraxane (squamous and non-squamous patients)	Abraxane 100mg/m^2 Carboplatin AUC 5 or 6	Abraxane and Carboplatin both IV infusions	Abraxane on Days 1, 8, and 15 of each 21-day cycle. Carboplatin on Day 1 of each 21-day cycle	4 cycles
Gemcitabine + cisplatin (squamous patients only)	Gemcitabine 1000 or 1250 mg/m^2 Cisplatin 75 mg/m^2	Gemcitabine and Cisplatin both IV infusions	Gemcitabine on Days 1 and 8 of each 21-day cycle Cisplatin on Day 1 of each 21-day cycle	4 cycles
Gemcitabine + carboplatin (squamous patients only)	Gemcitabine 1000 or 1250 mg/m^2 Carboplatin AUC 5 or 6	Gemcitabine and Carboplatin both IV infusions	Gemcitabine on Days 1 and 8 of each 21-day cycle Carboplatin on Day 1 of each 21-day cycle	4 cycles
Pemetrexed + carboplatin (non-squamous patients only)	Pemetrexed 500 mg/m^2 Carboplatin AUC 5 or 6	Pemetrexed and Carboplatin both IV infusions	Pemetrexed on Day 1 of each 21-day cycle then Pemetrexed maintenance every q3 or q4 weeks Carboplatin on Day 1 of each 21-day cycle	4 cycles then Pemetrexed maintenance until objective disease progression, unless contraindicated per the Investigator
Pemetrexed + Cisplatin (non-squamous patients only)	Pemetrexed 500 mg/m^2 Cisplatin 75 mg/m^2	Pemetrexed and Cisplatin both IV infusions	Pemetrexed on Day 1 of each 21-day cycle then Pemetrexed maintenance every q3 or q4 weeks Cisplatin on Day 1 of each 21-day cycle	4 cycles then Pemetrexed maintenance until objective disease progression, unless contraindicated per the Investigator

Dosing Scheme

Treatment arms	**During chemotherapy 1 cycle=3 weeks (21 days)**				**Post-chemotherapy 1 cycle=4 weeks (28 days)**		
	Cycle 1 Week 0	**Cycle 2 Week 3**	**Cycle 3 Week 6**	**Cycle 4 Week 9**	**Week 12**	**Week 16**	**Week 20 to PD**
Durva + Treme + SoC	Durva + Treme + SoC	Durva + Treme + SoC	Durva + Treme + SoC	Durva + Treme + SoC	Durva + Pemetrexed Maintenance	Durva + Treme Pemetrexed Maintenance	Durva + Pemetrexed Maintenance

4.2 Immunotherapy Toxicities and Dosing Delays/Dose Modifications

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for Durvalumab and Tremelimumab are provided in the Durvalumab and Tremelimumab Toxicity Management Guidelines (TMGs) (**Appendix B**).

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the immune-related adverse events (imAE). Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

All toxicities will be graded according to NCI CTCAE, Version 5.0.

4.2.1 Chemotherapy Toxicities and Dosing Delays/Dose Modifications

Chemotherapies are associated with a number of unwanted effects. Chemotherapy-related toxicity management and dose adjustment, including dose delays and reductions, should be performed as indicated in the local prescribing information for the relevant agent. In the event of unfavorable tolerability, patients can switch between cisplatin and carboplatin therapy at any point on study (assuming eligibility for the switched therapy is met).

In the event that an AE can reasonably be attributed to chemotherapy, dose adjustment of chemotherapy should be attempted before modifying the administration of Durvalumab ± Tremelimumab.

In the event that chemotherapy is delayed, Durvalumab ± Tremelimumab should also be delayed. Every effort should be made to ensure patients receive at least 4 cycles of chemotherapy across all treatment arms in the study, if conditions allow.

All toxicities will be graded according to NCI CTCAE, Version 5.0.

4.3 Concomitant Medications/Treatments

Patients on this study are mandated to receive concurrent chemotherapy, in addition to Durvalumab and Tremelimumab, with adherence to standard of care regimens, but is not mandated. Patients on this study should not be on any targeted systemic therapies such as those directed at *EGFR* mutations, *ALK* or *ROS1* gene rearrangements, *BRAF* V600E mutation, or *NTRK* gene fusions. Other anti-cancer treatments are also not allowed on the study and are listed in the table below. Supportive medications may be given at any point during treatment at the discretion of the treating physician, such as anti-emetics, pain medications, anti-diarrheas, nutritional supplementations, and anti-depressants. Anti-oxidant medications in excess of daily recommended values are not allowed.

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent radiotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the IO infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs, • Use in patients with contrast allergies. • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).
EGFR tyrosine kinase inhibitors (TKI)	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of Durvalumab or Tremelimumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when Durvalumab has been given concomitantly.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

4.4 Use of Contraception for Study Participants

4.4.1 Female patient of child-bearing potential

Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 highly effective method of contraception from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days (about 3 months)) after the last dose of Durvalumab monotherapy). Non-sterilized male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. 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.

4.4.2 Male patients with a female partner of childbearing potential

Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days (about 3 months) after the last dose of Durvalumab monotherapy). However, periodic 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.

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

4.4.3 Post-menopausal status considerations

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.

- 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.

4.4.4 Contraceptive methods

Highly effective methods of contraception are defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Note that 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).

Examples:

- Non-Hormonal
    - Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the participant)
    - Vasectomised sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia)
    - Tubal occlusion

- Intrauterine device (provided coils are copper-banded)

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

4.4.5 Blood donation

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

4.5 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for two years or until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the subject unacceptable for further treatment in the judgment of the investigator.

4.5.1 Subject Withdrawal

In the event a subject chooses to withdraw from the study, document if the subject is withdrawing from treatment only (and willing to be included in follow-up data collection), or if they are withdrawing from all study participation. For subject safety, the subject should be encouraged to return per the Schedule of Assessments in Appendix B

Notify the Principal Investigator/Sponsor-Investigator and document the reason for withdrawal from study and the date of discontinuation

4.6 Duration of Follow Up

Subjects will be followed for a period of 2 years after completion of radiation treatment or until death, whichever occurs first. Specifically, subjects will be followed at 1, 3, 6, 9, 12, 15, 18, 21, and 24 months following treatment. After the 2 year follow up, the patient can continue routine follow up with their physicians, per standard of care. Telehealth follow up office visits are acceptable. Subjects removed from therapy for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4.7 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 6.5 apply. Notify the Principal Investigator and document the reason for treatment discontinuation and the date of discontinuation. The subject should be followed-up per protocol.

4.8 Subject Replacement

Subjects may be replaced if they are removed from protocol therapy such as inadequate or unacceptable receipt of treatment. Replacement of subjects must be reviewed by the principal investigator.

5.0 RADIATION THERAPY TREATMENT PLAN

5.1 Stereotactic Radiation Therapy

5.1.1 Radiation therapy, either stereotactic ablative radiotherapy (SAbR) or Personalized Ultra-Fractionated Stereotactic Adaptive Radiotherapy (PULSAR), will be delivered with the targeting planning, and directing of treatment fields guided to a target based on known 3D coordinates related to reliable fiducial markers. This differs from conventional radiation therapy in which treatment is guided by skin or bony landmarks assumed to correlate to the target volume based on the initial simulation. Treatment will account for inter-/intra-fractional errors with careful dosimetry that delivers an ablative dose to the metastatic lesion(s) while respecting normal tissue constraints.

5.1.2 Radiation Therapy Prescription Dose

The treating radiation oncologist can choose to deliver 3 or 5 fractions depending on the clinical circumstances, i.e. anatomical location and adjacent organs-at-risk. Each radiation therapy fraction will encompass the 95% of the planning target volume and is considered compliant to the protocol. The following table lists the acceptable number of fractions and dose per fraction. Any dose delivered that is beyond the recommended doses will be considered an unacceptable variation. Isotoxic doses were calculated using the Universal Survival Model using H460 *Homo sapiens* lung carcinoma cell line data [68].

Number of fractions	Dose per fraction	Total dose
3	12 – 15.5 Gy	36 – 46.5 Gy
5	8 - 10 Gy	40 – 50 Gy

For tumors of the spine, given the close proximity of the spinal cord, a different dose-fractionation would be acceptable, as deemed appropriate by the treating physician. A dose of 30 Gy in 3 fractions or 40 Gy in 5 fractions would be acceptable.

5	8 Gy	40 Gy

5.1.3 Prescription Interval

For patients randomized to the SAbR arm, patients will receive each fraction of radiation therapy twice a week, with at least 24 hours between each treatment fraction, until the completion of the prescribed number of fractions. **SAbR should be scheduled to deliver the final fraction 24-48 hours prior to the first cycle of chemoimmunotherapy (preferably 24 hours prior).** Treatment delays are allowed for adverse events.

For patient randomized to the PULSAR arm, each PULSAR fraction is to be delivered every 3 weeks until the completion of the prescribed number of fractions. **Each pulse should be delivered 24-48 hours prior to a cycle of chemoimmunotherapy (preferably 24 hours prior).** PULSAR may be held if the patient does not have any targetable disease. Each PULSAR treatment and date of treatment delivery will be recorded.

5.1.4 Radiation Treatment Concerns and Concurrent Medications

Corticosteroid medications for inflammatory conditions can be used at the discretion of the treating oncologist (in which case, its use needs to be reported). However, use of corticosteroid medications are generally discouraged, given its immunosuppressive properties. Analgesic premedication to avoid general discomfort during long treatment durations is recommended when appropriate.

5.2 Technical Factors and Considerations

5.2.1 Physical Factors

Only photon (x-ray) beams produced by linear accelerators with photon energies of 4-15 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed. Restriction of photon beam energies > 10 MV but less than 15 MV will be based on clinical appropriateness taking into account distance the beam must travel to the target.

5.2.2 Dose Verification at Treatment

In-vivo dosimeter measurements (e.g., diode, TLD) may be obtained for surface dose verification for accessible beams. This information is not required by the protocol.

5.2.3 Treatment Platforms

The trial allows most commercially available photon or proton producing treatment units. Treatment units should include image guidance. Both 3D conformal and intensity-modulated radiation therapy (including volumetric-modulated arc therapy (VMAT)) are allowed. Proton or other charged particle units are not allowed in this study. Other specialized accelerators (e.g., the CyberKnife® or Tomotherapy) are allowed as long as they meet the technical specifications of the protocol.

5.3 Simulation and Image Guidance

5.3.1 Patient Positioning

Patients will be positioned in a stable position that allows accurate reproducibility of the target between treatments. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be utilized including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients external contours) with reference to the stereotactic coordinate system. Patient immobilization must be reliable enough to insure that the Gross Tumor Volume (GTV) does not deviate beyond the confines of the Planning Treatment Volume (PTV) with any significant probability (i.e. < 5%).

At the time of simulation for patients who will receive SBRT to the lung, liver, or other targets likely to move greater than 0.5 cm with respiration, the movement of the dome of the diaphragm (superior portion of the liver) is to be observed under fluoroscopy or other acceptable means to estimate respiratory movement during

treatment if no breathing control device is used. Patients will be assessed for suitability for tolerance of a respiratory control device using a breath-hold technique, respiratory gating, or abdominal compression to limit diaphragmatic excursion during respiration. Patients with severe lung disease and patients who cannot tolerate diaphragmatic or breathing control devices for other reasons will be treated without them. A larger margin to account for breathing related intra-fractional organ movement is required but no greater than a margin of 1.5 cm.

5.3.2 Image Guidance

Isocenter or reference point port localization images should be obtained on the treatment unit immediately before treatment to ensure proper alignment of the geometric center (i.e. isocenter) of the simulated fields. These IGRT images can be obtained with planar kV imaging devices or cone-beam CT equipment. For treatment systems that use kV imaging but also allow EPID imaging using the treatment beam, orthogonal images verifying the isocenter also should be obtained.

5.4 Treatment Planning and Target Volumes

5.4.1 Image Acquisition

Computed tomography will be the primary image platform for targeting and treatment planning. The planning CT scans must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting. CT scan with IV contrast is recommended unless the patient has allergy to contrast or renal insufficiency. Oral GI contrast to highlight the stomach and duodenum is recommended for patients with medial liver lesions or lesions of the caudate lobe. Axial acquisitions will be required with spacing ≤ 3.0 mm between scans. Images will be transferred to the treatment planning computers.

5.4.2 Target Volumes

The target lesion will be outlined by an appropriately trained physician and designated the gross tumor volume (GTV). The target will generally be drawn using appropriate windowing based on location of the metastatic lesion(s). 4-dimensional CT image guided GTV delineation to take tumor motion into consideration will be allowed.

For treatment to the lung, the target will generally be drawn using CT pulmonary windows; however, soft tissue windows with contrast may be used to avoid inclusion of adjacent vessels, atelectasis, or mediastinal or chest wall structures within the GTV. This target will not be enlarged whatsoever for prophylactic treatment (including no “margin” for presumed microscopic extension); rather, include only abnormal CT signal consistent with gross tumor (i.e., the GTV and the clinical target volume [CTV] are identical). An additional 0.5 cm in the axial plane and 0.5 in the longitudinal plane (craniocaudal) will be added to the GTV to constitute the PTV.

For treatment to the liver, the following structures are contoured: entire liver, each individual liver gross tumor volume (GTV), each kidney, small bowel, large, bowel, duodenum, stomach, and the spinal cord. The planning target volume (PTV) is constructed to account for the positional uncertainty of the GTV during treatment with a PTV margin of 0.5 cm is recommended. Larger margins may be used in cases where greater motion of the hemidiaphragm is observed in simulation despite standard maneuvers to diminish motion. 4-dimensional CT image acquisition is recommended to be utilized to evaluate for motion, and

motion management techniques such as breath hold or abdominal compression can be utilized at the discretion of the treating physicians. Fiducial markers can also be utilized to facilitate image guidance if available at the institution.

Treatment to skeletal and paraspinous lesions may be accomplished with any 3D conformal radiotherapy or intensity-modulated radiotherapy technique suitable for this application with performance specifications adequate to provide proper tumor dose distribution and normal tissue sparing.

5.5 Dosimetry

5.5.1 3D Conformal Planning

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Generally, more beams are used for larger lesion sizes. For this protocol, the isocenter is defined as the common point of gantry and couch rotation for the treatment unit. Prescription lines covering the PTV will typically be the 60-90% line (rather than 95-100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The isocenter in stereotactic coordinates will be determined from system fiducials (or directly from the tumor in the case of volumetric imaging) and translated to the treatment record.
The treatment dose plan will be made up of multiple static beams or arcs as described above. The plan should be normalized to a defined point corresponding closely to the center of mass of the PTV (COMPTV). Typically, this point will be the isocenter of the beam rotation; however, it is not a protocol requirement for this point to be the isocenter. Regardless, the point identified as COMPTV must have defined stereotactic coordinates and receive 100% of the normalized dose. Because the beam apertures coincide nearly directly with the edge of the PTV (little or no added margin), the external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning typically around 80% but ranging from 60-90%. The prescription dose will be delivered to the margin of the PTV. As such, a “hotspot” will exist within the PTV centrally at the COMPTV with a magnitude of prescribed dose times the reciprocal of the chosen prescription isodose line (i.e., 60-90%).

5.5.2 Intensity Modulated Radiation Therapy (IMRT)

IMRT, including volumetric-modulated arc therapy (VMAT) and modulated charged particles is allowed in this study. The use of IMRT in this study is at the discretion of the treating physician. However, IMRT should be considered only when target coverage, OAR dose limits, or dose spillage are not achievable with 3D conformal planning. In addition, IMRT plans should follow the same planning principles as discussed above for 3D conformal planning. The number of segments (control points) and the area of each segment should be optimized to ensure deliverability and avoid complex beam fluences. Ideally, the number of segments should be minimized, and the area of each segment should be maximized (the aperture of one segment from each beam should correspond to the projection of the PTV along a beam’s eye view).

5.5.3 Dose Calculations

For purposes of dose planning and calculation of monitor units for actual treatment, this protocol will require tissue density heterogeneity correction.

Successful treatment planning will require accomplishment of all of the following criteria:

1. 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.
2. Prescription isodose: The prescription isodose surface must be ≥ 60% and < 90% of the maximum dose.
3. Prescription Isodose Surface Coverage: The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface (PTV V95%RX = 100%) and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose (PTV V90%RX > 99%).

5.6 Normal Tissue Dose Constraints

5.6.1 The following table lists the specific organ and dose fractionation constraints on normal tissue. Given the irregular, long intervals between each radiotherapy fraction, total dose will be calculated to a particular organ-at-risk to ensure safety of radiation therapy. Exceeding these dose tolerances by more than 2.5% constitutes a minor protocol violation. Exceeding these dose tolerances by more than 5% constitutes a major protocol violation.

One Fraction

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**	Endpoint (≥Grade 3)
Optic Pathway	<0.2 cc	8 Gy	10 Gy	neuritis
Cochlea			9 Gy	hearing loss
Brainstem (not medulla)	<0.5 cc	10 Gy	15 Gy	cranial neuropathy
Spinal Cord and medulla	<0.35 cc	10 Gy	14 Gy	myelitis
Cauda Equina	<5 cc	14 Gy	16 Gy	neuritis
Sacral Plexus	<5 cc	14.4 Gy	16 Gy	neuropathy
Esophagus*	<5 cc	20 Gy	24 Gy	esophagitis
Brachial Plexus	<3 cc	13.6 Gy	16.4 Gy	neuropathy
Heart/Pericardium	<15 cc	16 Gy	22 Gy	pericarditis
Great vessels	<10 cc	31 Gy	37 Gy	aneurysm
Trachea and Large Bronchus*	<4 cc	27.5 Gy	30 Gy	impairment of pulmonary toilet
Bronchus- smaller airways	<0.5 cc	17.4 Gy	20.2 Gy	stenosis with atelectasis
Rib	<5 cc	28 Gy	33 Gy	Pain or fracture
Skin	<10 cc	25.5 Gy	27.5 Gy	ulceration
Stomach	<5 cc	17.4 Gy	22 Gy	ulceration/fistula
Bile duct			30 Gy	stenosis
Duodenum*	<5 cc	17.4 Gy	22 Gy	ulceration
Jejunum/Ileum*	<30 cc	17.6 Gy	20 Gy	enteritis/obstruction
Colon*	<20 cc	20.5 Gy	31 Gy	colitis/fistula
Rectum*	<3.5 cc <20 cc	30 Gy 23 Gy	33.7 Gy	proctitis/fistula
Ureter			35 Gy	stenosis
Bladder wall	<15 cc	12 Gy	25 Gy	cystitis/fistula
Penile bulb	<3 cc	16 Gy		impotence
Femoral Heads	<10 cc	15 Gy		necrosis
Renal hilum/vascular trunk	15 cc	14 Gy		malignant hypertension

Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc for males and 950cc for females***	7.2 Gy		Basic Lung Function
Lung (Right & Left)			V-8Gy <37%	Radiation Pneumonitis
Liver	700 cc***	11.6 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc***	9.5 Gy		Basic renal function

***Avoid circumferential irradiation.**
**** "point" defined as 0.035cc or less.**
*****or one third of the "native" total organ volume (prior to any resection or volume reducing disease), whichever is greater.**

Three Fraction

Serial Tissue	**Volume**	**Volume Max (Gy)**	**Max Point Dose (Gy)****	**Endpoint (≥Grade 3)**
Optic Pathway	<0.2 cc	15.3 Gy	17.4 Gy	neuritis
Cochlea			14.4 Gy	hearing loss
Brainstem (not medulla)	<0.5 cc	15.9 Gy	23.1 Gy	cranial neuropathy
Spinal Cord and medulla	<0.35 cc	15.9 Gy	22.5 Gy	myelitis
Cauda Equina	<5 cc	21.9 Gy	25.5 Gy	neuritis
Sacral Plexus	<5 cc	22.5 Gy	25.5 Gy	neuropathy
Esophagus*	<5 cc	27.9 Gy	32.4 Gy	esophagitis
Brachial Plexus	<3 cc	22 Gy	26 Gy	neuropathy
Heart/Pericardium	<15 cc	24 Gy	30 Gy	pericarditis
Great vessels	<10 cc	39 Gy	45 Gy	aneurysm
Trachea and Large Bronchus*	<5 cc	39 Gy	43 Gy	impairment of pulmonary toilet
Bronchus- smaller airways	<0.5 cc	25.8 Gy	30 Gy	stenosis with atelectasis
Rib	<5 cc	40 Gy	50 Gy	Pain or fracture
Skin	<10 cc	31 Gy	33 Gy	ulceration
Stomach	<5 cc	22.5 Gy	30 Gy	ulceration/fistula
Bile duct			36 Gy	stenosis
Duodenum*	<5 cc	22.5 Gy	30 Gy	ulceration
Jejunum/Ileum*	<30 cc	20.7 Gy	28.5 Gy	enteritis/obstruction
Colon*	<20 cc	28.8 Gy	45 Gy	colitis/fistula
Rectum*	<3.5 cc <20 cc	43 Gy 30.3 Gy	47 Gy	proctitis/fistula
Ureter			40 Gy	stenosis
Bladder wall	<15 cc	17 Gy	33 Gy	cystitis/fistula
Penile bulb	<3 cc	25 Gy		impotence
Femoral Heads	<10 cc	24 Gy		necrosis
Renal hilum/vascular trunk	15 cc	19.5 Gy		malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**

Lung (Right & Left)	1500 cc for males and 950cc for females***	10.8 Gy		Basic Lung Function
Lung (Right & Left)			V-11.4Gy<37%	Pneumonitis
Liver	700 cc***	17.7 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc***	14.7 Gy		Basic renal function

***Avoid circumferential irradiation.**
**** "point" defined as 0.035cc or less.**
*****or one third of the "native" total organ volume (prior to any resection or volume reducing disease), whichever is greater.**

Five Fraction

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**	Endpoint (≥Grade 3)
Optic Pathway	<0.2 cc	23 Gy	25 Gy	neuritis
Cochlea			22 Gy	hearing loss
Brainstem (not medulla)	<0.5 cc	23 Gy	31 Gy	cranial neuropathy
Spinal Cord and medulla	<0.35 cc	22 Gy	28 Gy	myelitis
Cauda Equina	<5 cc	30 Gy	31.5 Gy	neuritis
Sacral Plexus	<5 cc	30 Gy	32 Gy	neuropathy
Esophagus*	<5 cc	32.5 Gy	38 Gy	esophagitis
Brachial Plexus	<3 cc	27 Gy	32.5 Gy	neuropathy
Heart/Pericardium	<15 cc	32 Gy	38 Gy	pericarditis
Great vessels	<10 cc	47 Gy	53 Gy	aneurysm
Trachea and Large Bronchus*	<5 cc	45 Gy	50 Gy	impairment of pulmonary toilet
Bronchus- smaller airways	<0.5 cc	32 Gy	40 Gy	stenosis with atelectasis
Rib	<5 cc	45 Gy	57 Gy	Pain or fracture
Skin	<10 cc	36.5 Gy	38.5 Gy	ulceration
Stomach	<5cc	26.5 Gy	35 Gy	ulceration/fistula
Bile duct			41 Gy	stenosis
Duodenum*	<5 cc	26.5 Gy	35 Gy	ulceration
Jejunum/Ileum*	<30 cc	24 Gy	34.5 Gy	enteritis/obstruction
Colon*	<20 cc	32.5 Gy	52.5 Gy	colitis/fistula
Rectum*	<3.5 cc <20 cc	50 Gy 37.5 Gy	55 Gy	proctitis/fistula
Ureter			45 Gy	stenosis
Bladder wall	<15 cc	20 Gy	38 Gy	cystitis/fistula
Penile Bulb	<3 cc	30 Gy		impotence
Femoral Heads	<10 cc	30 Gy		necrosis
Renal hilum/vascular trunk	15 cc	23 Gy		malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc for males and 950cc for females***	12.5 Gy		Basic Lung Function

Lung (Right & Left)			V-13.5Gy<37%	Pneumonitis
Liver	700 cc***	21.5 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc***	17.5 Gy		Basic renal function

***Avoid circumferential irradiation.**
**** "point" defined as 0.035cc or less.**
*****or one third of the "native" total organ volume (prior to any resection or volume reducing disease), whichever is greater.**

5.7 Radiation Therapy Quality Assurance

Dr. Badiyan will perform a radiation therapy quality assurance review after complete data of the first 10 cases enrolled at the University of Texas Southwestern Medical Center followed by a final review after complete data for the remaining cases are completed. These cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received, whichever occurs first.

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 60 days prior to registration into the study unless otherwise stated. The screening procedures include:

6.1.1 **Informed Consent**

6.1.2 **Medical history**

Complete medical and surgical history, history of infections, PD-L1 status (can be performed if not obtained before). Any ongoing signs/symptoms present during screening should be assessed and graded per CTCAE and followed as per section 8.

6.1.3 **Demographics**

Age, gender, race, ethnicity

6.1.4 **Review subject eligibility criteria.**

6.1.5 **Review previous and concomitant medications.**

6.1.6 **Physical exam including vital signs, height and weight.**

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

6.1.7 **Performance status**

Performance status evaluated prior to study entry according to Appendix A.

6.1.8 **12-lead electrocardiogram**

In triplicate, 2-5 minutes apart

6.1.9 **Hematology**

If screening clinical chemistry and hematology assessments are performed within 14 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.

6.1.10 **Serum chemistries**

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, amylase, lipase, total bilirubin, TSH, coagulation (PT, PTT, INR), hepatitis serologies, HIV, and urinalysis

If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at day 1. Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system. Reflex TSH testing can be utilized to automatically trigger free T4 and/or free T3, in the event that TSH levels are abnormal.

If screening clinical chemistry and hematology assessments are performed within 14 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.

6.1.11 **Tumor assessment**

Patient must have CT of the chest, abdomen, and pelvis and/or PET/CT, which can be performed within 90 days prior to registration. Contrast can be used but also may be withheld if the patient has a verified allergy to iodinated contrast or poor kidney function. MR of the brain can also be obtained to rule out the presence of brain metastases, if feasible.

6.2 Procedures During Treatment

6.2.1 **Prior to Each Treatment Cycle**

- Physical exam
- Body weight
- Vital signs
- Assessment of performance status
- Laboratory testing
  - Results for LFTs, electrolytes, complete blood count, and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or Investigator prior to dosing.
- Administration of Durvalumab or Tremelimumab
- Patient reported questionnaires

6.2.2 **30 days after treatment termination**

- Physical exam, vital signs
- Hematology
- Serum chemistries

6.3 Follow-up Procedures

Subject will be followed every three months (+/- 2 weeks) after completion of (or early withdrawal from) study treatment until month 24:

- Dedicated imaging, including CT of sites of known disease or PET/CT, will be performed prior to each follow up visit

- Additional personalized radiotherapy will be delivered, if deemed appropriate by treating radiation oncologist
- Palliative re-irradiation using conventional fractionation regimens are allowed, if deemed appropriate by the treating radiation oncologist
- Physical exam and vital signs not required if visit is conducted via telehealth.

6.4 Timeline of Events

Please see Schedule of Assessment (**Appendix B**)

6.5 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

6.5.1 Subject voluntarily withdraws from treatment (follow-up permitted)

6.5.2 Subject withdraws consent (termination of treatment and follow-up), see section 4.5.1

Patients are free to withdraw from the study at any time (IP and assessments) without prejudice to further treatment. Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

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

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

- All further participation in the study including any further follow up (eg, survival contact telephone calls)
- Withdrawal to the use of any samples

6.5.3 Subject is unable to comply with protocol requirement

6.5.4 Subject demonstrates disease progression (unless continued treatment with study drug/treatment is deemed appropriate at the discretion of the investigator)

6.5.5 Subject experiences toxicity that makes continuation in the protocol unsafe

6.5.6 Treating physician determines continuation on the study would not be in the subject's best interest

6.5.7 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event)

6.5.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study

6.5.9 **Lost to follow-up:** Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact

with a missing patient is re-established, the patient should not be considered lost to follow-up, and evaluations should resume according to the protocol.

In order to support key endpoints of PFS and OS analyses, the survival status of all patients in the full analysis and the safety analysis sets should be re-checked, this includes those patients who withdrew consent or are classified as “lost to follow up.”

- Lost to Follow up – site personnel should check hospital records, the patients’ current physician, and a publicly available death registry (if available) to obtain a current survival status. (The applicable CRF modules will be updated.)
- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status. (The applicable CRF modules will be updated.)

6.5.10 Discontinuation of study treatment, for any reason, does not impact the patient’s participation in the study. A patient who decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any AE. The patient should continue attending subsequent study visits, and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This follow-up could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter follow-up (see Schedule of Assessments (SoA)).

Patients who permanently discontinue drug for reasons other than objective iRECIST disease progression should continue to have RECIST scans performed every 3 months until iRECIST-defined radiological PD plus an additional follow-up scan or death (whichever comes first) as defined the SoAs. If a patient is discontinued for iRECIST-defined progression, then the patient should have 1 additional follow-up scan performed preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD.

All patients will be followed for survival until the end of the study.

Patients who decline to return to the site for evaluations should be contacted by telephone as indicated in the SoAs as an alternative.

Patients who have permanently discontinued from further receipt of IP will need to be discontinued from the IVRS/IWRS.

7.0 MEASUREMENT OF EFFECTS

7.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria called iRECIST which is a modified Response Evaluation Criteria in Solid Tumors to evaluate response in patients treated with immunotherapy [69, 70]. Changes in only

the largest diameter (unidimensional measurement) of the tumor lesions are used in the iRECIST criteria.

7.1.1 Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with study therapy.

Evaluable for objective response. Only those subjects who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

7.1.2 Disease Parameters

Measurable Disease: Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

1. 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
2. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
3. 20 mm by chest x-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease.
All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Target lesions.
All measurable lesions representative of all involved organs should be identified as target lesions.

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

For iRECIST, there is no change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline).

7.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 90 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

7.1.4 Response Criteria

7.1.4.1 Evaluation of Target Lesions

iRECIST is based on RECIST 1.1. Responses assigned using iRECIST have a prefix of “i” (ie, immune)—eg, “immune” complete response (iCR) or partial response (iPR), and unconfirmed progressive disease (iUPD) or confirmed progressive disease (iCPD) to differentiate them from responses assigned using RECIST 1.1. Similar nomenclature is used for stable disease (iSD). New lesions are assessed and subcategorised into those that qualify as target lesions (new lesion, target) or non-target lesions (new lesion, non-target). Patients can have iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD.

Complete Response (iCR): Disappearance of all target lesions. Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be “0” if there are target nodes). Determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions, as per RECIST 1.1.

Partial Response (iPR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions, as per RECIST 1.1.

Progressive Disease (iPD): >20% increase in the SLD taking as reference the smallest SLD recorded since the treatment started (nadir) and minimum 5 mm increase over the nadir, as per RECIST 1.1.

Stable Disease (iSD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started. There can be no unequivocal new lesions, as per RECIST 1.1.

While on study, should a chosen Target lesion become non-evaluable, document as Not Evaluable (NE)

New lesions: Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD.

Confirmation of progression guidelines are set for the following reasons:
• for patient management and treatment decisions
• in the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic iRECIST assessment of progressive disease (PD) in order to distinguish pseudoprogression from true radiologic progression, also known as iRECIST modified for confirmation of progression
• when scans are evaluated by Investigator and by BICR, to reduce informative censoring by Investigator assessments (Investigator assesses PD at a time-point earlier than does BICR).

Confirmed objective disease progression refers to either of the following scenarios: 1. clinical progression/deterioration followed by a radiologic verification scan (iPD by iRECIST); or 2. in the absence of significant clinical deterioration, radiologic iPD by iRECIST followed by a second radiologic confirmation scan with iPD assessed according to the specific confirmation of progression criteria listed below. iRECIST modified for confirmation of progression refers to the second scenario above. The confirmatory scan should occur preferably at the next scheduled imaging visit and no earlier than 4 weeks following the date of the immediate prior assessment of iRECIST iPD.

Immediate prior radiologic progression would be considered confirmed if any the following criteria are met in the confirmatory scan:
• ≥20% increase in the sum diameters of target lesions (TLs) compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in sum of diameters compared to nadir,
• and/or significant progression (worsening) of non-target lesions (NTLs) and/or of pre-existing new lesions at the confirmatory scan time-point compared with the immediate prior time-point (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan time-point),
• and/or additional new unequivocal lesions at the confirmatory scan time-point.

NOTE: In order to have confirmed objective disease progression, there should be two consecutive assessments meeting the iPD definition: the first iPD by iRECIST and the second PD using the confirmation of progression criteria (above). If the first assessment fulfilling the iPD definition by iRECIST is not confirmed, continue with assessments until the next iPD by iRECIST, which in turn will need its own immediate subsequent confirmation scan. In the absence of significant clinical deterioration, treatment with study drug may continue between the initial assessment of progression and the scan to confirm progression.

If the confirmation scan confirms progression, then the date of the prior scan with iPD should be declared as the date of progression.
If progression is not confirmed, in the absence of significant clinical deterioration, then the patient should continue study drug and on-treatment assessments until the next iPD which will also require a follow-up confirmation scan. If the first iPD is not confirmed by the immediate next scan, then the Investigator should not change the I PD assessment of the first scan.

If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) prior to radiologic progression, then the patient should still continue to be followed until confirmed objective disease progression.

7.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Incomplete Response/Stable Disease (Non-CR/Non-PD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

While on study, should a chosen Non-Target lesion become non-evaluable, document as Not Evaluable (NE).

7.1.4.3 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). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

	Timepoint response with no previous iUPD in any category	**Timepoint response with previous iUPD in any category***
Target lesions: iCR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be

	Timepoint response with no previous iUPD in any category	Timepoint response with previous iUPD in any category*
		unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same. Previously identified in assessment immediately before this timepoint. “i” indicates immune responses assigned using iRECIST. iCR=complete response. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression. non-iCR/non-iUPD=criteria for neither CR nor PD have been met. iCPD=confirmed progression. RECIST=Response Evaluation Criteria in Solid Tumours.

7.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for iCR or iPR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall iCR is measured from the time measurement criteria are first met for iCR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

7.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the time from random assignment to disease progression or death from any cause.

7.2 Safety and Tolerability

Analyses will be performed for all subjects having received at least one dose of study therapy, of either immunotherapy or radiotherapy. The study will use the CTCAE version 5.0 for reporting of adverse events.
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see the SoAs).

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and

sample sizes may vary depending on the laboratory method used and routine practice at the site. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

Laboratory Testing

The laboratory variables to be measured are presented in the following tables. Other safety tests to be performed at screening include assessment for hepatitis B surface antigen, hepatitis C antibodies, and HIV antibodies.

The following laboratory variables will be measured:

Hematology Laboratory Tests

Hemoglobin	Platelet count
Absolute lymphocyte	Total white cell count
Absolute neutrophil count	

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 0 (unless all screening laboratory haematology assessments are performed within 14 days prior to cycle 1, day 1), and as clinically indicated. Can be recorded as absolute counts or as percentages. Absolute counts will be calculated by DM if entered as percentage. Total white cell count therefore has to be provided.

Clinical Chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase
Amylase	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen,
Gamma glutamyltransferase[b]	depending on local practice

Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.

It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable.

Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, and magnesium testing are to be performed at baseline, on Day 1 (unless all screening laboratory clinical chemistry assessments are performed within 14 days prior to Day 1), and if clinically indicated.

Creatinine Clearance will be calculated by data management using Cockcroft-Gault (using actual body weight).

If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at day Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system

Urinalysis Tests

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red blood cells

If a patient shows an AST or ALT ≥3xULN together with total bilirubin ≥2xULN, refer to **Appendix C** for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

All patients should have further chemistry profiles performed at 30 days (±3 days), 2 months (±1 week) and 3 months (±2 weeks) after permanent discontinuation of IP Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from IP must have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

Physical Examinations

Physical examinations will be performed according to the assessment schedules (see the SoAs). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 8. Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position. In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding. Situations in which ECG results should be reported as AEs are described. At screening, a single ECG will be obtained on which QTcF must be <470 ms. In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding. Situations in which ECG results should be reported as AEs are described in Section 8.

Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the SoAs. Body weight is also recorded at each visit along with vital signs.

During treatment administration

First infusion

On the first infusion day, patients will be monitored, and vital signs collected/recorded in eCRF prior to, during and after infusion of IP as presented in the bulleted list below. BP and pulse will be collected from patients in the IO arms before, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion])
- Approximately 30 minutes during the infusion (**halfway** through infusion)
- At the end of the infusion (approximately 60 minutes ±5 minutes)
- If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if

clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab or tremelimumab.

Subsequent infusions
Blood pressure, pulse, and other vital signs should be measured, collected/recorded in eCRF prior to the start of the infusion. Patients should be carefully monitored and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. It is recommended that patients are contacted 2 weeks after receiving the first 3 cycles of durvalumab + tremelimumab or durvalumab monotherapy (Cycle 1 Day 14, Cycle 2 Day 14, and Cycle 3 Day 14) of study drug(s) to ensure early identification and management of toxicities.

Performance Status
WHO/ECOG Performance will be assessed using the table in **Appendix A.**

8.0 ADVERSE EVENTS

8.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial and are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline or is stable in the opinion of the investigator;
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death.

8.1.1 Definitions

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding, or clinically significant laboratory finding), symptom, clinical event, or disease, temporally associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

An AE includes but is not limited to any clinically significant worsening of a patient's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (i.e., occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that

begins after written informed consent has been obtained but before the patient has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the patient being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.
The term AE is used to include both serious and non-serious AEs.

Acute Adverse Events
Adverse events occurring in the time period from the signing of the informed consent, through 90 days (about 3 months) post treatment will be considered acute adverse events.

Late Adverse Events
Adverse events occurring in the time period from the end of acute monitoring, to 24 months (2 years post treatment), will be defined as late adverse events. These events are define below as Adverse Events of Special Interest (AESI).

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. An AESI may be serious or non-serious.

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

AESIs (Adverse Events of Special Interest) observed with durvalumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis / transaminase increases.
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases.
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g., Guillain-Barré, and myasthenia gravis)
- Intestinal Perforations
- Psoriasis

AESIs (Adverse Events of Special Interest) observed with durvalumab plus tremelimumab combination therapy include:

- Rash / Dermatitis
- Diarrhea / Colitis
- Hepatic events
- Endocrinopathies (i.e. events of hypophysitis, thyroiditis, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Pancreatic events
- Pneumonitis
- Renal events

- Infusion/hypersensitivity reaction
- Myositis
- Myocarditis
- Intestinal Perforations
- Neuropathy / neuromuscular toxicity (e.g., Guillain-Barré, and myasthenia gravis)
- Psoriasis

Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to:

- Pericarditis
- Sarcoidosis
- Uveitis
- Other events involving the eye and skin.
- Hematological events
- Rheumatological events
- Vasculitis
- Non-infectious meningitis
- Non-infectious encephalitis.

It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

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

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochure. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see **Appendix C**). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening.
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event.

Serious Adverse Events

OHRP and UTSW HRPP define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- is life-threatening (places the subject at immediate risk of death from the event as it occurred).

- Results in inpatient hospitalization[1,2] or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health, and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.
    - Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations, or development of drug dependency or drug abuse.
    - Adverse Events (AEs) for malignant tumors reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a Non-Serious AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.
    - The above instruction applies only when the malignant tumor event in question is a new malignant tumor (i.e., it is not the tumor for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring ≥24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated potentially reported as SAEs.

[2]NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visits where a patient is admitted for observation or minor treatment (e.g., hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

8.1.2 **Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):**

The phrase “unanticipated problems involving risks to subjects or others” is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied.

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up
All adverse events will be followed up according to good medical practices.

8.2 Steps to Characterize a Serious Adverse Event for Reporting to the SCCC DSMC

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *may NOT be related* to the study treatment.

- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported as indicated in the sections below.

Step 4: Determine the expectedness of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable);
- the drug package inserts (if applicable).
- the current Investigator's Brochure (if applicable)
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol.

8.2.1 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

SAEs and UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs occurring during the protocol-specified monitoring period and all UPIRSOs should be submitted to the SCCC DSMC within 5 business days of the study team members awareness of the event(s). In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events or unanticipated.
Problems.

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

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

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in RedCap.

AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

In addition, the following variables will be collected for SAEs as applicable:

- AE (verbatim)
- The date when the AE started and stopped.
- The maximum CTCAE grade reported.
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)

- Action taken with regard to IPs.
- Administration of treatment for the AE
- Outcome

In addition, the following variables will be collected for SAEs:
- Date the AE met criteria for SAE.
- Date the Investigator became aware of the SAE.
- Seriousness criteria fulfilled.
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 8
- Description of the SAE

The grading scales found in the NCI CTCAE version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

Study recording period and follow-up for adverse events and serious adverse events if a patient discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

The investigator is responsible for following all SAEs until resolution, until the patient returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

The UTSW study PI is responsible for ensuring SAEs/UPIRSOs are submitted to the SCCC DSMC Coordinator. This may be facilitated by the IIT project manager, study team, sub-site or other designee. Electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC.

UT Southwestern and affiliates will submit documentation via the SAE submission portal. All subsites participating in multi-center study may utilize the Serious Adverse Event Template and submit to the IIT Project Manager, or designee. The DSMC Coordinator will route the form to the DSMC Chair who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE or UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required via the same process. *(See Appendix V of the SCCC DSMC Plan for instructions on how to submit SAEs through the portal and for a template Serious Adverse Event Form which may be utilized).*

DSMC Chairperson reviews all SAEs and UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and

either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to: Sarah Neufeld, MS, MBA, Clinical Research Manager (214) 648-1836
Written reports to: Department of Radiation Oncology Clinical Research Office The University of Texas Southwestern Medical Center Attention: Sarah Neufeld, MS, MBA, Clinical Research Manager 2280 Inwood Rd. Dallas, Texas 75390-9303 Fax: (214) 648-1836 Email: Sarah.Hardee@UTSouthwestern.edu UTSW SCCC Data Safety Monitoring Committee Coordinator Website for entering SAEs: https://utsouthwestern.inforeadv4.com/ UTSW Institutional Review Board (IRB) Submit a Reportable Event via eIRB with a copy of the final sponsor report as attached supporting documentation.

Overdose

An overdose is defined as a patient receiving a dose of Durvalumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study patient with Durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor. The sponsor must report these to AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox within 7 calendar days or sooner when required. If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. 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.

Hepatic function abnormality

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to the sponsor. The Sponsor must report these events to AstraZeneca Patient Safety using the designated Safety e-mailbox within 7 calendar days or sooner when required, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed. The criteria for a potential Hy's Law case is Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study patient will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study patient must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor and AstraZeneca/MedImmune.

Pregnancy

Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.
If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the sponsor within 1 day, i.e., immediately, but no later than 24 hours of when he or she becomes aware of it.

The sponsor will work with the Investigator to ensure that all relevant information is provided within 1 to 5 calendar days. The Sponsor must report to AstraZeneca Patient Safety using the designated Safety e-mailbox within 7 calendar days or sooner when required, for pregnancies with SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days (about 6 months) after the last dose of Durvalumab, Tremelimumab + any drug combination therapy or 90 days (about 3 months) after the last dose of Durvalumab and/or Tremelimumab, whichever is the longer time period.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days (about 6 months) after the last dose of Durvalumab, Tremelimumab + any drug combination therapy or 90 days (about 3 months) after the last dose of Durvalumab and/or Tremelimumab, whichever is the longer time period should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner.

The Sponsor must report to AstraZeneca Patient Safety using the designated Safety e-mailbox within 7 calendar days or sooner when required.

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

UPIRSOs must be promptly reported to the UTSW HRPP within 5 working days of
PI awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of study team awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/hrpp/quality-assurance

8.3 Unblinding Procedures

Not applicable to this study.

8.4 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to **Appendix C**, the Toxicity

Management Guidelines, for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law

8.5 New Cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the patient's inclusion in this study.

8.6 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page.
- The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page.
- A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within a reasonable timeframe.
- Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined safety follow up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

AstraZeneca/MedImmune retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.7 Stopping Rules

There will be an early stopping rule for unexpected toxicity. If, at any point, during the study more than 1/6th of patients (at least 11 patients) treated to date experience study related grade 4 or 5 toxicity of any kind, study enrollment will be suspended. Depending on the nature of the toxicity and whether it is related to the use of immunotherapy or radiotherapy, the protocol may be amended to adjust dose parameters and be reviewed and reapproved by the Institutional Review Board. The study may also be stopped if there is a significant benefit of radiotherapy over the standard of care arm after review with the principal investigators and the Data Safety and Monitoring Committee.

8.8 Reporting of Serious Adverse Events to AstraZeneca

If the study is being conducted in multiple countries or multiple sites, Investigators or other site personnel inform Sponsor representatives of the SAE. The coordinating centre/Sponsor is responsible for informing Company of the SAE. All SAEs have to be reported to Company, whether or not considered causally related to the investigational product.

SAEs related to the Investigational Product (IP) must be provided to Company in an ongoing basis as individual case reports.

At the end of the Study a final unblinded summary line listing of all SAEs notified to the regulatory authority and/or Company during the Study, must be provided to the Company to enable reconciliation of safety information held by Company for its product(s).

Send SAE reports (individual case reports and line listings) and accompanying cover page to Company (TCS) via Email: AEmailboxclinicaltrialTCS@astrazeneca.com

SAEs that do not require expedited reporting to the Regulatory Authority/IRB/IEC still need to be reported to Company.

Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported to Company at the same time these events are notified to the Regulatory Authority.
In the case of blinded trials, Company may request that the Sponsor either provide a copy of the randomization code/code break information or unblind those SAEs which require expedited reporting.

8.9 Reporting of Deaths to AstraZeneca

All deaths must be recorded and reported. In addition, all SAEs resulting in death or death of unknown cause must be reported to AstraZeneca via AEMailboxClinicalTrialTCS@AstraZeneca.com within 7 calendar days of awareness or sooner when required.

9.0 DRUG/TREATMENT INFORMATION

9.1 Durvalumab

- Other names for the drug(s): Imfinzi, MED4736
- Classification - type of agent: Antineoplastic agent, immune checkpoint inhibitor
- Mode of action: Anti-PD-1 monoclonal antibody
- Supply and Storage: Durvalumab will be supplied by AstraZeneca as a 500-mg vial concentrate for solution for infusion. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The nominal volume is 10 mL.

  Durvalumab is a sterile, clear to opalescent, colorless to slightly yellow solution, free from visible particles.

  Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Investigational product must be kept in original packaging until use to prevent prolonged light exposure.
- Protocol dose: 1500 mg every 4 weeks
- Preparation and Administration: The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the vial to the start of administration must not exceed:
  - 24 hours at 2°C to 8°C (36°F to 46°F)
  - 8 hours at room temperature

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hrs.

A dose of 1500 mg (for patients >30 kg in weight) 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 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30.0 mL (i.e. 1500 mg) of durvalumab to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time is 1 hour, however if there are interruptions, the total allowed time must not exceed 8 hours at room temperature.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered. Infusion time does not include the final flush time.

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

- Monitoring: Patients will be monitored before, during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment. Patients are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped). In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion related reaction is Grade 3 or higher in severity, study drug will be discontinued. Standard infusion time is one hour, however if there are interruptions, the total allowed time must not exceed 8 hours at room temperature (otherwise requires new infusion preparation). For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines in **Appendix C**. As with any antibody, allergic reactions to dose administration are possible. 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. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

- Incompatibilities: None identified

- Availability: Commercially available and provided by sponsor

- Side effects: The most common adverse reactions were fatigue, musculoskeletal pain, constipation, decreased appetite, nausea, peripheral edema, and urinary tract infection. The most common Grade 3 or 4 adverse reactions (≥3%) were fatigue, urinary tract infection, musculoskeletal pain, abdominal pain, dehydration, and general physical health deterioration.

- Return of durvalumab: Unopened vials of durvalumab lyophilised or liquid Drug Product must be stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Unopened vials that is no longer needed will be returned to the study sponsor or disposed using proper biohazard procedure.

9.2 Tremelimumab

- Other Names: CP-675,206
- Classification: Anti-CTLA-4 monoclonal antibody
- Mode of Action: Tremelimumab is specific for human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), a cell surface receptor that is expressed primarily on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 or CD86 ligands on antigen-presenting cells. Tremelimumab blocks the inhibitory signal resulting from CTLA-4 binding to CD80/86, leading to prolongation and enhancement of T-cell activation and expansion.
- Description: Tremelimumab is a human immunoglobulin G2 kappa (IgG2κ) monoclonal antibody.
- How Supplied: Tremelimumab is supplied by AstraZeneca, and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as single-use 400 mg/vial solution for infusion (20 mg/mL). Tremelimumab solution for infusion is formulated in 20 mM histidine/histidine-HCl, 222 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, and 0.27 mM disodium edetate dihydrate, pH 5.5.
- Preparation: Tremelimumab solution for infusion must be diluted prior to administration. Allow the required number of vials to equilibrate to room temperature for 30 minutes. Do not shake the vials. To prepare the infusion solution add the dose volume of tremelimumab to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP and mix by gentle inversion to ensure homogeneity of the dose in the bag. The final concentration must be between 0.10 mg/mL to 10 mg/mL. Polycarbonate syringes should not be used with tremelimumab. Saline bags must be latex-free and can be made of polyvinyl chloride (PVC) or polyolefins (eg, polyethylene), manufactured with bis (2-ethylhexyl) phthalate (DEHP) or DEHP free.
- Storage: Store intact vials between 2-8°C (36-46°F). Do not freeze. If a storage temperature excursion is identified, promptly return tremelimumab to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.
- Stability: Stability testing of the intact vials is on-going. Total in-use storage time from needle puncture of tremelimumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8°C (36-46°F). If there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.
- Route of Administration: IV infusion
- Method of Administration: Infuse over approximately 60 minutes using IV infusion lines made of PVC/DEHP or PVC/trioctyl trimellitate (TOTM) or polyethylene or

polyurethane. All DEHP-containing or DEHP-free lines are acceptable. IV lines should contain a 0.22 or 0.2 µm in-line filter. The in-line filter can be made of polyethersulfone or polyvinylidine fluoride. IV lines containing cellulose-based filters should not be used with tremelimumab. Flush the IV line with a volume of normal saline equal to the priming volume of the infusion set used at the completion of infusion. Do not co-administer other drugs through the same infusion line.

- Availability: Tremelimumab is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Tremelimumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This study is a prospective single-center, randomized phase II trial. The primary endpoint on this study will be global health status/quality of life (QoL) and symptom burden, determined by the global health status/quality of life score on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) at 3 months after treatment.

We hypothesize that the combination of durvalumab, tremelimumab, and stereotactic radiotherapy, in the form of SAbR and PULSAR, will confer an improvement in quality of life over the historical control of the use of palliative radiotherapy in advanced non-small cell lung cancer, as determined by the [**Appendix D**].

Secondary endpoints include local control at one year, out-of-field control at one year, overall response rate at 12 weeks, progression-free survival, overall survival, and toxicity.

Local control is defined as the percentage of tumors without tumor failure within the irradiated field, as defined as growth on diagnostic imaging studies or evidence of viable cancer cells. Out-of-field control is defined as the percentage of tumors without tumor failure outside of the irradiated field, as defined as growth on diagnostic imaging studies or evidence of viable cancer cells. Overall response rate is defined as complete response and partial response at 12 weeks (about 3 months) from randomization. Progression-free survival (PFS) is defined as the time from random assignment to disease progression or death from any cause. Overall survival (OS) is defined as the defined as the time between the date of randomization and the date of death due to any cause. Toxicity will be assessed using the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0).

10.2 Sample Size and Accrual

We assume that a significant improvement in quality of life (QoL) is defined as a rate of ≥ 10% improvement in QoL, which has been shown in validation studies to correlate with “moderate” improvement. Based on prior data of palliative radiotherapy in patients with metastatic cancer, the proportion of historical controls experiencing a positive change of ≥ 10% is 33% [50, 71].

Each of the treatment arms will be compared to the historical control rate of 33%. We hypothesize that a treatment arm will have 60% improvement in QoL. A sample size of 23 patients in each arm is needed to detect a difference of 27% (= 60% - 33%) using a two-sided exact binomial test with a two-sided significance level of 0.1 and 80%

power. We will enroll 26 patients per arm, and accounting for 10% attrition, the total evaluable sample size is 52 patients.

We will also analyze response to treatment based on the stratification variable, bone versus non-bone metastases, as the location of the metastasis may have differing immunostimulatory effects as well as PD-L1 status (as a percentage positive by immunohistochemistry), separated into values of 0, ≥1-49%, ≥50%.

10.3 Randomization Scheme

Patients will be allocated to the treatment using a permuted block randomization with site of metastases (bone versus non-bone) and PD-L1 (0, ≥1-49%, ≥50%) status as a stratum, in a ratio of 1:1, to either SabR arm or the PULSAR arm, with 26 patients allocated to each treatment arm.

10.4 Analysis Plans

All eligible patients who are randomized to the study will be included in the comparison of treatment arms, regardless of treatment compliance, that is, intent-to-treat analysis. Progression-free survival, overall survival, local control, and out-of-field control will be estimated using the Kaplan-Meier method. The log-rank test will be used to test for a statistically significant difference in survival distributions. The null and alternative hypotheses are H_0: $S_1(t) = S_2(t)$ versus H_A: $S_1(t) \neq S_2(t)$, where $S_i(t)$ is the distribution of progression-free survival times for patients in arm i. The Cox proportional hazard regression model will be used to determine hazard ratios and 95% confidence intervals for the treatment difference in progression-free survival. Unadjusted ratios and ratios adjusted for covariates of interest will be computed.

For safety of radiotherapy, only adverse events assessed to be definitely, probably, or possibly related to protocol treatment will be considered. The rates of all Grade 3-5 adverse events and death during or within 30 days of discontinuation of protocol treatment will be computed. Descriptive statistics will be computed for the duration of maintenance of chemotherapy, and time to initiation of third line systemic agent.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB of record will have the proper representation and function in accordance with federally mandated regulations. The IRB of record must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been

provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

11.3 Registration/Randomization Procedures

All subjects consenting to participate in any aspect of the trial must be registered on REDCap before initiating protocol activities. The eligibility checklist and confirming documentation will be entered electronically through the system. All research data will be recorded and entered into Case Report Forms using REDCap. Following registration, research staff from Clinical Research Office will review all relevant data to ensure eligibility criteria have been met.

New subjects will receive a number beginning with 001 upon study consent such that the first subject consented is numbered 001, the second subject consented receives the number 002, et cetera. Upon confirmation of eligibility and enrollment as per the aforementioned instructions, the subject will be assigned a secondary number in the order of enrollment. For example, subject 001 will become 001-01 upon enrollment. If subject 002 screen fails, and subject 003 is the next subject enrolled, subject 003 will become 003-02 and so on.

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration/randomization code according to the numbering schema outlined above, which should then be entered as the patient study ID in Velos upon updating the status to enrolled.

The numbering schema should clearly identify the site number; the sequential number of the subject consented as well as the status of the subjects enrolled so that the number of subjects consented versus the number of subjects actually enrolled may be easily identified.

11.4 Data Management and Monitoring/Auditing

11.4.1 **Data Management**

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements, as appropriate for the project.

11.4.2 **Trial Monitoring**

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT, which includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

11.4.3 **Trial Audits**

Toxicity and reviews will be performed at least annually. These reviews will be documented by Disease Oriented Team, which includes but is not limited to

accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries, and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the SCCC DSMC reviews all local serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

11.5 Adherence to the Protocol

Except for an emergency situation, in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

Any deviation from the protocol requirements, whether pre-approved or unexpected, are to be recorded/logged as a protocol deviation and reported per institutional policy.

11.5.1 **Exceptions** (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; and/or
- in the investigator's control; and/or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)
    - **Reporting requirement***: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation. For eligibility waivers, studies which utilize the SCCC-DSMC as the DSMC of record must also obtain approval from the DSMC prior to submitting to IRB for approval.

11.5.2 **Emergency Deviations:** include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, and/or
- protect the life or physical well-being of subjects or others
- **Reporting requirement*:** Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

11.5.3 **Serious Noncompliance** (formerly called major deviations or **violations**): include any departure from IRB-approved research that:

- Increase risk of harm to subjects; and/or
- adversely affects the rights, safety, or welfare of subjects (any of which may also be an unanticipated problem); and/or
- adversely affects the integrity of the data and research (i.e., substantially compromises the integrity, reliability, or validity of the research)
- **Reporting requirement***: Serious Noncompliance must be promptly reported to the IRB within 5 working days of discovery

11.5.4 **Continuing Noncompliance:** includes a pattern of repeated noncompliance (in one or more protocols simultaneously, or over a period of time) which continues **after** initial discovery, including inadequate efforts to take or implement corrective or preventive action within a reasonable time frame.

➢ **Reporting requirement***: Continuing Noncompliance must be promptly reported to the IRB within 5 working days of discovery.

11.5.5 **Noncompliance (that is neither serious nor continuing; formerly called minor deviations) any departure from IRB-approved research that:**

- Does not meet the definition of serious noncompliance or continuing noncompliance

  ➢ **Reporting requirement***: Noncompliance that is neither serious nor continuing should be tracked and summarized at the next IRB continuing review, or the notice of study closure- whichever comes first.

*Reporting Requirements reflect UTSW HRPP/IRB guidelines; participating sites should follow the reporting guidelines for their IRB of record

11.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory and essential documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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APPENDICES

12.1 Appendix A – ECOG Performance Scale

ECOG PERFORMANCE SCALE

0 Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).

1 Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).

3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).

4 Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).

5 Death (Karnofsky 0).

12.2 Appendix B – Schedule of Assessments

	Screening and Randomization		**Follow Up**							
Cycle			**1**		**2**	**3**	**4**	**5**		
Day	**-30 to -1**	**-15 to -1**	**1**	**2**	**22**	**43**	**64**	**85**	**Every month[b]**	**Every 3 months**
Week	**-4 to -1**	**-3 to -1**	**0**		**3**	**6**	**9**	**12**		
				+/- 3 days					**+/- 14 days**	
Written informed consent/assignment of patient identification number	X									
Verify eligibility criteria	X									
Randomization	X									
History	X				X	X	X	X	X	
Medical history	X				X	X	X	X	X	
Demographics	X									
Performance status assessment	X				X	X	X	X	X	
Physical examination (vital signs, height, body weight)	X				X	X	X	X	X	
Review of previous and concomitant medications	X									
Patient questionnaires	X				X	X	X	X		X
Laboratory testing (CBC, serum chemistries, liver function)	X				X	X	X	X	X	
PD-L1 testing	X									
Thyroid stimulating hormone	X									
Electrocardiogram	X									
Hepatitis B and C and HIV serologies	X									
Coagulation panel (PT, PTT, INR)	X									
Urinalysis	X									
Tumor assessment	X						X			X
Administration of chemotherapy			X		X	X	X	X[e]	X[e]	
Administration of Durvalumab			X		X	X	X	X	X[b]	
Administration of Tremelimumab			X		X	X	X		X[b]	

Administration of SAbR (if assigned)		X[c]								
Administration of PULSAR (if assigned)		X[d]			X[d]	X[d]	X[a,d]	X[a,d]		
Assessment of adverse events				X	X	X	X	X	X	X

[a]If receiving 5 fractions
[b]An additional dose of Durvalumab and Tremelimumab will be given at Week 16 post-chemotherapy. In the case of dose delay(s), more than 1 Durvalumab and Tremelimumab combination dose can be given at and after Week 16 post-chemotherapy to ensure that up to 5 combination doses are administered.
[c] SAbR should be delivered so that the final fraction is delivered 24-48 hours prior to administration of chemoimmunotherapy (preferably 24 hours prior)
[d] PULSAR should be delivered so that the pulse of radiation is delivered 24-48 hours prior to administration of chemoimmunotherapy (preferably 24 hours prior)
[e] If receiving maintenance pemetrexe

12.3 Appendix C – Durvalumab Toxicity Management Guidelines (version 28 Oct 2022)

Toxicity Management Guidelines (TMGs)	
Drug Substance	Durvalumab and Tremelimumab
TMG Version	21 September 2023

ANNEX TO PROTOCOL

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy

Note: Annex is to be used in any clinical trial protocol within which patients are treated with Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy

Modification / Update, MOD014-STU-2021-0171, Shahed Badiyan, 6/8/2025

Version History

September 2023

The Toxicity Management Guidelines (TMGs) have been developed to assist investigators with the recognition and management of toxicities associated with use of the immune-checkpoint inhibitors durvalumab [MEDI4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanism of toxicities observed with these two compounds, these TMGs are applicable to the management of patients receiving either drug as monotherapy or both drugs in combination. Additionally, these guidelines are applicable when either durvalumab or tremelimumab or a combination of these two immune checkpoint inhibitors (ICI) is used in combination with other anti-cancer drugs (e.g., antineoplastic chemotherapy, targeted agents). These other anticancer drugs can be administered concurrently or sequentially as part of a protocolspecific treatment regimen. The TMGs provide information for the management of immunemediated reactions, infusion-related reactions, and non-immune-mediated reactions that may be observed with monotherapy or combination ICI regimens, with specific instructions for ICI dose modifications (including discontinuation) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other anti-cancer treatment.

Dosing modification and toxicity management for immune-mediated, infusion-related, and nonimmune–mediated reactions associated with the use of a checkpoint inhibitor or checkpoint inhibitors in clinical study protocol (CSP) – whether that is durvalumab alone, tremelimumab alone, or durvalumab + tremelimumab in combination, or durvalumab +/- tremelimumab in combination with other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) administered concurrently or sequentially – should therefore be performed in accordance with this Annex to CSP, which for the purposes of submission and approval of substantial updates is maintained as a standalone document. TMG updates are iterated by date, and should be used in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version specified in the CSP.

Although the TMG versioning is independent of the protocol, the TMG Annex to Protocol should be read in conjunction with the Clinical Study Protocol, where if applicable additional references for the management of toxicities observed with other anti-cancer treatment are included in the specific section of the Clinical Study Protocol.

General Considerations Regarding Immune-Mediated Reactions

These guidelines are provided as a recommendation to support investigators in the management of potential immune-mediated adverse eve

Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated r
advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., National Comprehensive Cancer Network (
of Medical Oncology (ESMO)) in the management of these events. Refer to the section of the table titled "Other -Immune-Mediated Reactions
imAEs not noted in the "Specific Immune-Mediated Reactions" section.
Early identification and management of imAEs is essential to ensure safe use of the study drug. Monitor patients closely for symptoms and
manifestations of underlying imAEs. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies
concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-m
management promptly, including specialty consultation as appropriate. In general, withhold study drug/study regimen for severe (Grade 3) imAEs
study drug/study regimen for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatme
corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.
Based on the severity of the imAE, durvalumab and/or tremelimumab should be withheld and corticosteroids administered. Upon improvement to
should be tapered over ≥ 28 days. More potent immunosuppressive agents should be considered for events not responding to systemic steroids. Alter
agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines. With l
immunosuppressive use, consider the need for glucose monitoring.
Dose modifications of study drug/study regimen should be based on severity of treatment-emergent toxicities graded per NCI CTCAE version in the

Considerations for Prophylaxis for Long Term use of Steroids for Patients Receiving Immune Checkpoint Inhibitor Immunotherapy

- **Infection Prophylaxis: Pneumocystis jirovecii pneumonia (PJP), antifungal and Herpes Zoster reactivation**
- **Gastritis: Consider prophylaxis for patients at high risk of gastritis (e.g. NSAID use, anticoagulation) when the patient is taking steroid**
- **Osteoporosis: Consider measures for prevention and mitigation of osteoporosis .**

Relevant Society Guidelines for Management of imAEs

These society guidelines are provided as references to serve in support of best clinical practice and the TMGs. Please note, these were the cu guidelines at the time of updating TMGs. Please refer to the most up to date version of these guidelines.

1. Brahmer JR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adver Cancer 2021;9:e002435
2. Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: An Clinical Oncology (ASCO) Guideline Update. J Clin Oncol 2022;39(36):4073-4126.
3. Haanen J, et al. Management of toxicities from immunotherapy: European Society for Medical Oncology (ESMO) clinical practice guide treatment, and follow-up. Annals Oncol 2022;33(12):1217-1238.
4. Sangro B, et al. Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma. J Hepatol 2020;72
5. Thompson JA, et al. National Comprehensive Cancer Network Guidelines: Management of immunotherapy-related toxicities version 2.2 28, 2022.

Pediatric Considerations Regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTCAE grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks of** initiating corticosteroids.	– All recommendations for specialist consultation shou specialist in the specialty recommended. – The recommendations for steroid dosing (i.e., mg/k patients should also be used for pediatric patients. – The recommendations for intravenous immun plasmapheresis use provided for adult patients may b patients. – The infliximab 5 mg/kg IV one time dose recommen as recommended for pediatric patients ≥ 6 years ol and dosing in children < 6 years old, consult a pedia – For pediatric dosing of mycophenolate mofetil, cons – With long-term steroid and other immunosuppressiv PJP prophylaxis, gastrointestinal protection, and glu

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Mana
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any G** – Patients should be thorough any alternative etiology presentation (e.g. infection, – Monitor patients for signs symptoms of pneumonitis worsening shortness of br patients with imaging and including other diagnostic below. – Suspected pneumonitis sho radiographic imaging an disease-related etiologies e described below. – Initial work-up may incl monitoring of oxygenati (resting and exertion), labor clinically relevant culture infection), and high- tomography (CT) scan. – Consider Pulmonary and consults.
	Grade 1	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1** – Monitor and closely follow clinical symptoms, pulse exertion), and laboratory clinically indicated.
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1.	**For Grade 2** – Monitor symptoms

		If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper (≤10 mg prednisone or equivalent).	consider hospi indicated. – Consider Pulmonary and Consults; – Promptly start systemic ste to 2 mg/kg/day PO or IV e Consider HRCT or chest CT imaging study as clinically – If no improvement within workup should be conside with IV methylprednisol started. – If no improvement within methylprednisolone at 2 t start immunosuppressive necrosis factor (TNF) inhi 5 mg/kg IV once, may be after initial dose at the provider or relevant practi is important to rule o infliximab label for gener infliximab. – Consider discussing with Cli

	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Hospitalize the patient – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with Clinical Study Lead, as needed. – Consider starting anti-infective therapy if infection is still a consideration on the basis of other diagnostic testing despite negative culture results – Supportive care (e.g., oxygen). – If no improvement within 2 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for *Clostridium difficile* toxin, etc. – 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). – Consider further evaluation with imaging study with contrast. – Consult a gastrointestinal (GI) specialist for consideration of further workup. – **WHEN SYMPTOMS OR EVALUATION INDICATE AN INTESTINAL PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY.** – **PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION.** – 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 events, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide, and other supportive care measures. – If symptoms persist, consider checking lactoferrin and/or calprotectin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 – If toxicity improves to Grade ≤1, then study drug/study regimen can be	**For Grade 2** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes

		resumed after completion of steroid taper (<10 mg prednisone, or equivalent).	(e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Consider further evaluation with imaging study with contrast. – Consider consult of a gastrointestinal (GI) specialist for consideration of further workup. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 days despite therapy with 1 to 2 mg/kg IV methylprednisolone, reconsult GI specialist and, if indicated, promptly start additional immunosuppressant agent such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines. **Caution: it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.** – **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.** – Consider, as necessary, discussing with Clinical Study Lead if no resolution to Grade ≤1 in 3 to 4 days.
	Grade 3 or 4	**Grade 3** – For patients treated with durvalumab monotherapy, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper (≤10 mg prednisone per day, or equivalent). – For patients treated with durvalumab in combination with other products (not tremelimumab), decision to be made at the discretion of the study	**For Grade 3 or 4** – Urgent GI consult and imaging and/or colonoscopy as appropriate. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – If still no improvement within 2 days, continue steroids and promptly add further immunosuppressants. (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.

		investigator, in discussion with AstraZeneca Clinical Study Lead. **For patients treated with durvalumab in combination with tremelimumab or tremelimumab monotherapy:** **A. Permanently discontinue tremelimumab for Grade 3 diarrhea/colitis. HOLD durvalumab until resolution to Grade ≤ 1; durvalumab alone can be resumed after completion of steroid taper (<10 mg prednisone per day or equivalent)** **B. Permanently discontinue both durvalumab and tremelimumab for 1) Grade 4 diarrhea/colitis or 2) Any grade of intestinal perforation** **Grade 4** Permanently discontinue study drug/study regimen.	– **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.**
Hepatitis ***Infliximab should not be used for management of immune-related hepatitis.*** **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in hepatocellular carcinoma**	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications). – Monitor and evaluate transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP]) and total bilirubin .
	ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN	– No dose modifications. – If it worsens, then consider holding therapy.	– Continue transaminase and total bilirubin monitoring per protocol.
CONT **secondary tumour involvement of the liver with abnormal baseline values [BLV])**	ALT or AST > 3 ≤ 5 x ULN or total bilirubin > 1.5 ≤ 3 x ULN	– Hold study drug/study regimen dose until ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN. Resume study drug/study regimen after completion of steroid taper (<10 mg prednisone or equivalent). – Permanently discontinue study drug/study regimen for any case meeting Hy's law laboratory criteria (AST or ALT >3 × ULN AND	– Regular and frequent checking of transaminases and total bilirubin (e.g., every 1 to 2 days) until transaminases and total bilirubin elevations improve or resolve. - Consider checking creatinine phosphokinase (CPK) and aldolase (to rule out myositis) – If no resolution to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN in 1 to 2 days, consider discussing with Clinical Study Lead, as needed.

		bilirubin ≥2 × ULN without initial findings of cholestasis (i.e., elevated ALP) and in the absence of any alternative cause.	– If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	ALT or AST > 5- ≤ 10 x ULN	– Hold study drug/study regimen. Resume study drug/study regimen if elevations downgrade to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN after completion of steroid taper (<10 mg prednisone, or equivalent). – **If in combination with tremelimumab, do not restart tremelimumab.**	– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. - Check CPK and aldolase (to rule out myositis) – Perform Hepatology Consult, abdominal workup, and imaging as appropriate. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.**
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN ALT or AST > 10 x ULN OR total bilirubin > 3 x ULN	Permanently discontinue study drug/study regimen.	– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.** – Perform Hepatology Consult, abdominal workup, and imaging as appropriate.
Hepatitis **(elevated transaminases and total bilirubin)** ***Infliximab should not be used for management of immune-related hepatitis.***	**Any Elevations of AST, ALT, or T. Bili as Described Below**	**General Guidance**	**For Any Elevations Described** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – Monitor and evaluate AST, ALT, ALP, and T. Bili. – For hepatitis B (HBV) + patients: evaluate quantitative HBV viral load, quantitative Hepatitis B surface antigen (HBsAg), or Hepatitis B envelope antigen (HBeAg).

THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients (or secondary tumour involvement of the liver with abnormal baseline values [BLV])			– For hepatitis C (HCV) + patients: evaluate quantitative HCV viral load. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HBV medications if HBV viral load is >2000 IU/ml. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HCV medications if HCV viral load has increased by ≥2-fold. – For HCV+ with Hepatitis B core antibody (HBcAb)+: Evaluate for both HBV and HCV as above.
See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	Isolated AST or ALT >ULN and ≤2.5×BLV,	– No dose modifications. – If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. – For all transaminase elevations , see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	
	ALT or AST > 2.5-≤ 5X BLV and ≤ 20xULN	– Hold study drug/study regimen dose until resolution to AST or ALT ≤2.5×BLV . – If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤2.5×BLV , resume study drug/study regimen after completion	– Regular and frequent checking of Transaminases and total bilirubin (e.g., every 1 to 3 days) until elevations of these are improving or resolved. - Consider checking creatinine phosphokinase (CPK) and aldolase (to rule out myositis) – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with Clinical Study Lead.

		of steroid taper (<10 mg prednisone, or equivalent).	– If event is persistent (>2 to 3 days) or worsens, and investigator suspects toxicity to be an imAE, start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup. If still no improvement within 2 to 3 days despite 2mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting additional immunosuppressants. (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss Clinical Study Lead if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	ALT or AST >5-7X BLV and ≤ 20X ULN OR concurrent 2.5-5X BLV and ≤ 20XULN AND total bilirubin > 1.5 - < 2 x ULN	- Withhold durvalumab and permanently discontinue tremelimumab – Resume study drug/study regimen if elevations downgrade to AST or ALT ≤2.5×BLV and after completion of steroid taper (<10 mg prednisone, or equivalent). – Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤2.5×BLV within 14 days	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. - Check CPK and aldolase (to rule out myositis) – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider discussing with Clinical Study Lead, as needed. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an additional immunosuppressant. (e.g.,., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with a hepatologist or relevant practice guidelines). Discuss with Study Clinical Lead if mycophenolate is not available. **Infliximab should NOT be used.**

	ALT or AST > 7 X BLV OR > 20 ULN whichever occurs first OR bilirubin > 3ULN	Permanently discontinue study drug/study regimen.	**Same as above (except recommend obtaining liver biopsy early)**
Nephritis and/or renal dysfunction	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). – Consider Consulting a nephrologist. – Consider imaging studies to rule out any alternative etiology – 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, decreased urine output, or proteinuria). Follow urine protein/creatinine ratio every 3-7 days
	Grade 1	No dose modifications.	**For Grade 1** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider hydration, electrolyte replacement, and diuretics, as clinically indicated. – Consider nephrologist consult if not resolved within 14 days, or earlier as clinically indicated
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion	**For Grade 2** – Consider including hydration, electrolyte replacement, and diuretics as clinically indicated – Follow urine protein/creatinine ratio every 3-7 days – Carefully monitor serum creatinine as clinically warranted.

		of steroid taper (<10 mg prednisone, or equivalent).	– Consult nephrologist and consider renal biopsy if clinically indicated. – Start prednisone 0.5 – 1 mg/kg/day if other causes are ruled out – If event is persistent beyond 5 days or worsens, increase to prednisone up to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup. When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Carefully monitor serum creatinine daily. – Follow urine protein/creatinine ratio every 3-7 days – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days of steroids or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant
Dermatologic Adverse Events (Including Pemphigoid)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology. – Monitor for signs and symptoms of dermatitis (rash and pruritus). **HOLD STUDY DRUG IF GRADE 3 PEMPHIGOID OR SEVERE CUTANEOUS ADVERSE REACTION (SCAR)[1] IS SUSPECTED.**

			– **PERMANENTLY DISCONTINUE STUDY DRUG IF SCAR OR GRADE 3 PEMPIGOID IS CONFIRMED.**
	Grade 1	No dose modifications.	**For Grade 1** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emollient, lotion, or institutional standard).
	Grade 2	For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. – If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade 2** – Consider dermatology consult and skin biopsy, as indicated. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 1 week or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with Clinical Study Lead, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	Grade 3	**For Grade 3** – Hold study drug/study regimen until resolution to Grade ≤1 or baseline. – If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade** – Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor the extent of rash [Rule of Nines]. – Consider, as necessary, discussing with Clinical Study Lead.
	Grade 4	**For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 4** – Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.

			– Consider hospitalization. – Monitor the extent of rash [Rule of Nines]. Consider, as necessary, discussing with Clinical Study Lead.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Consider consulting an endocrinologist for endocrine events. – Consider discussing with Clinical Study Lead, as needed. – Monitor patients for signs and symptoms of endocrinopathies. (Non-specific symptoms include headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness.) – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: thyroid stimulating hormone (TSH), free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, hemoglobin A1c (HgA1c)). 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. – Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consulting an endocrinologist to guide

			assessment of early morning adrenocorticotropin hormone (ACTH), cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2, 3, or 4	– For Grade 2-4 endocrinopathies <u>other than hypothyroidism and type 1 diabetes mellitus (T1DM)</u>, consider holding study drug/study regimen dose until acute symptoms resolve. – Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper (<10 mg prednisone, or equivalent). – Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement.	**For Grade 2, 3, or 4** – 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 T1DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement. – **Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids.** – **Isolated T1DM may be treated with appropriate diabetic therapy, and without corticosteroids. <u>Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis.</u>** – For patients with normal endocrine workup (laboratory assessment or magnetic resonance imaging (MRI) scans), repeat laboratory assessments/MRI as clinically indicated.
Amylase/Lipase increased	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression, viral infection, concomitant medications, substance abuse). – 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. – Assess for signs/symptoms of pancreatitis – Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT) – If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase – If evidence of pancreatitis, manage according to pancreatitis recommendations
	Grade 1	No dose modifications.	
	Grade 2, 3, or 4	**For Grade 2, 3, or 4** In consultation with relevant gastroenterology specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology. – Consider Gastroenterology referral
	Grade 2	**Consider holding study drug/regimen**	**Grade 2** – Consider IV hydration – Consider Gastroenterology referral

	Grade 3, or 4	**For Grade 3** Hold study drug/study regimen until resolution of elevated enzymes and no radiologic findings If no elevation in enzymes or return to baseline values, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). **For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3, or 4** – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – IV hydration
Nervous System Disorders			
Aseptic Meningitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** – Symptoms may include headache, photophobia, and neck stiffness, nausea/ vomiting which may resemble an infectious meningitis. – Patients may be febrile. – Mental status should be normal	**For Any Grade** – Consider neurology consult – Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. – Exclude bacterial and viral infections. (ie HSV) - Consider antibiotic for bacterial coverage until cultures/panel results are back – Consider IV acyclovir until polymerase chain reactions are available
	Any Grade	Permanently discontinue study drug/study regimen	**For Any Grade** – Consider neurology consult – Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. – Exclude bacterial and viral infections. (ie HSV) – Consider IV acyclovir until polymerase chain reactions are available – Consider, as necessary, discussing with Clinical Study Lead. – Consider hospitalization.

			– Once infection has been ruled out promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.
Encephalitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** – Symptoms may include Confusion, altered behaviour, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality. –	**For Any Grade** – Consider neurology consult – Consider testing including MRI of the brain with and without contrast, lumbar puncture, electroencephalogram (EEG) to evaluate for subclinical seizures, ESR, CRP, antineutrophil cytoplasmic antibody (ANCA) (if vasculitic process suspected), thyroid panel including TPO and thyroglobulin and additional autoantibodies to rule out paraneoplastic disorders. – Exclude bacterial and viral infections. (i.e. HSV)Consider IV acyclovir until polymerase chain reactions are available.
	Grade 2	**For Grade 2** Permanently discontinue study drug/study regimen.	**For Grade 2** – Consider, as necessary, discussing with the Clinical Study Lead. – Once infection has been ruled out methylprednisolone 1–2 mg/kg/day – For progressive symptoms or if oligoclonal bands are present consider methylprednisolone 1 g IV daily for 3–5 days plus IVIG or plasmapheresis
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider, as necessary, discussing with Clinical Study Lead. – Consider hospitalization. – Once infection is ruled out, start methylprednisolone 1 g IV daily for 3–5 days for progressive symptoms consider adding IVIG or plasmapheresis
Demyelinating Disease (optic neuritis, transverse myelitis, acute demyelinating encephalomyelitis (ADEM))	**Any Grade**	**General Guidance** – Permanently discontinue immunotherapy – Consider MRI of the spine and brain	**For Any Grade** – Consider neurology consult – Inpatient care – Consider prompt initiation of high methylprednisolone pulse dosing – Strongly consider IVIG or plasmapheresis

		– Once imaging is complete, consider lumbar puncture Consider testing to rule out additional aetiologies: B12, copper, HIV, rapid plasma reagin (RPR), ANA, anti-Ro/La antibodies, aquaporin-4 IgG, myelin oligodendrocyte glycoprotein (MOG) IgG, paraneoplastic panel	
Peripheral neuropathy	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be evaluated to rule out any alternative etiology for neuropathy (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation.
	Grade 1	No dose modifications.	**For Grade 1** – Consider discussing with the Clinical Study Lead, as needed. – Monitor symptoms for interference with ADLS, gait difficulties, imbalance, or autonomic dysfunction
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 2** – Consult a neurologist. – Consider EMG/NCS

			– Consider discussing with the Clinical Study Lead, as needed. – Observation for additional symptoms or consider initiating prednisone 0.5–1 mg/kg orally – If progression, initiate methylprednisolone 2–4 mg/kg/day and treat as GBS – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider discussing with Clinical Study Lead, as needed. – Recommend hospitalization. – Monitor symptoms and consult a neurologist. – **Treat per Guillain-Barré Syndrome recommendations**
Guillain-Barré Syndrome (GBS)		General Guidance	– Recommend hospitalization – Obtain neurology consult – Obtain MRI of spine to rule out compression lesion – Obtain lumbar puncture – Antibody tests for GBS variants – Pulmonary function tests – Obtain electromyography (EMG) and nerve conduction studies – Frequently monitor pulmonary function tests and neurologic evaluations – Monitor for concurrent autonomic dysfunction – Initiate medication as needed for neuropathic pain
	Grade 2-4	Grade 2-4 Permanently discontinue	**Start IVIG or plasmapheresis in addition to methylprednisolone 1 gram daily for 5 days, then taper over 4 weeks.**
Myasthenia gravis		General Guidance	– Obtain neurology consult – Recommend hospitalization – Obtain pulmonary function tests

			– Obtain labs: ESR, CRP, creatine phosphokinase (CPK), aldolase and anti-striational antibodies – Consider cardiac exam, ECG, troponin, transthoracic echocardiogram for possible concomitant myocarditis – Obtain electromyography (EMG) and nerve conduction studies – Consider MRI of brain/spine to rule out CNS involvement by disease – Avoid medications that might exacerbate MG (e.g. beta blockers, some antibiotics, IV magnesium)
	Grade 2	Permanently discontinue	– Consider pyridostigmine 30mg three times daily and gradually increase based on symptoms (max dose 120mg four times daily) – Consider starting low dose prednisone 20mg daily and increase every 3-5 days. (Target dose 1mg/kg/day. Max dose 100mg daily)
	Grade 3-4	Permanently discontinue	– Start methylprednisolone 1-2mg/kg/day. Taper steroids based on symptom improvement – Start plasmapheresis or IVIG – Consider rituximab if refractory to plasmapheresis or IVIG – Frequent PFT assessments – Daily neurologic evaluations
Myocarditis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade** – Initial work-up should include clinical evaluation, B-type natriuretic peptide (BNP), cardiac enzymes, electrocardiogram (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) – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with

			baseline cardiopulmonary disease and reduced cardiac function. – Consider discussing with the Clinical Study Lead, as needed. – 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). Consult a cardiologist early, to promptly assess whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed.
	Grade 2, 3 or 4	– If Grade 2-4, permanently discontinue study drug/study regimen.	**For Grade 2-4** – Monitor symptoms daily, hospitalize. – Consider cardiology consultation and a prompt start of high-dose/pulse corticosteroid therapy – Supportive care (e.g., oxygen). – If no improvement consider additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab), IVIG or plasmapheresis or other therapies depending on the clinical condition of the patient, based on the discretion of the treating specialist consultant r or relevant practice guidelines. **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.**
Myositis/ Polymyositis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).

	defining the CTCAE grade/severity)		– 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, and; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the Clinical Study Lead. - **Consider that patients may present with or progress to rhabdomyolysis. Treat signs and symptoms as per institutional protocol or local clinical practice.** – Initial work-up should include clinical evaluation, **creatine kinase, aldolase**, lactate dehydrogenase (LDH), blood urea nitrogen (BUN)/creatinine, erythrocyte sedimentation rate or C-reactive protein (CRP) 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.
	Grade 1	– No dose modifications.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult.

		– Consider, as necessary, discussing with the Clinical Study Lead.
Grade 2	– Hold study drug/study regimen dose until resolution to Grade ≤1. – Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Consider Rheumatology or Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the Clinical Study Lead. – 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 2 to 3 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 days, consider additional – immunosuppressive therapy such as TNF inhibitors (e.g., infliximab), IVIG or plasmapheresis, or other therapies based on the discretion of the treating specialist consultant or relevant practice guideline **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**
Grade 3	**For Grade 3** – Hold study drug/study regimen dose until resolution to Grade ≤1. – Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30	**For Grade 3** – Monitor symptoms closely; recommend hospitalization. – Consider Rheumatology and/or Neurology consult – Consider discussing with the Clinical Study Lead, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant.

		days or if there are signs of respiratory insufficiency.	– If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.** – Consider whether patient may require IV IG, plasmapheresis.
	Grade 4	**For Grade 4** Permanently discontinue study drug/study regimen.	**Grade 4** – Monitor symptoms closely; recommend hospitalization. – Consider Rheumatology and/or Neurology consult – Consider discussing with the Clinical Study Lead, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**

[1] SCAR terms include Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Erythema Multiforme, Acute Generalized Exanthematous Pustulosis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Drug-induced hypersensitivity syndrome.

Other–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g. immune thrombocytopenia, haemolytic anaemia, uveitis, vasculitis).	– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections). – The Clinical Study Lead may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section – Consultation with relevant specialist – Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Monitor as clinically indicated
Grade 2	– Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. – If toxicity worsens, then treat as Grade 3 or Grade 4. – Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. – Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper	**For Grade 2, 3, or 4** Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and society guidelines. (See page 4).
Grade 3	Hold study drug/study regimen until resolution to Grade ≤1 or baseline	
Grade 4	Permanently discontinue study drug/study regimen	

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

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade** – Manage per institutional standard at the discretion of investigator. – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2** – The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. – Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. – Consider premedication per institutional standard or study protocol prior to subsequent doses. – Consider steroids for patients who have previously experienced infusion reaction; use of steroid premedication may be permitted in these situations
Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Manage severe infusion-related reactions per institutional standard, appropriate clinical practice guidelines, and society guidelines.

Non-Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2-3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

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

List of Abbreviations

AChE	Acetylcholinesterase	ILD	Interstitial lung disease
ACTH	Adrenocorticotropic hormone	imAE(s)	Immune-mediated adverse event(s)
ALT	Alanine aminotransferase	INR	International normalized ratio
ASCO	American Society of Clinical Oncology	IU	International units
AST	Aspartate aminotransferase	IV	Intravenous
(T) Bili	(Total) Bilirubin	IVIG	Intravenous immunoglobulin
BNP	B-type natriuretic peptide	LDH	Lactate dehydrogenase
BUN	Blood urea nitrogen	LFTs	Liver function tests
CRP	C-reactive protein	LLN	Lower limit of normal
CSP	Clinical Study Protocol	MRCP	Magnetic resonance cholangiopancreatography
CT	Computed tomography	MRI	Magnetic resonance imaging
CTCAE	Common Terminology Criteria for Adverse Events	NCCN	National Comprehensive Cancer Network
CTLA-4	Cytotoxic T-lymphocyte antigen-4	NCI	National Cancer Institute
DILI	Drug-induced liver injury	PD-L1	Programmed cell death ligand-1
ECG	Electrocardiogram	PJP	Pneumocystis jirovecii pneumonia
ECHO	Echocardiogram	PO	By mouth
ESMO	European Society of Medical Oncology	SCAR	Severe cutaneous adverse reaction
GI	Gastrointestinal	SITC	Society for Immunotherapy of Cancer
HBcAb	Hepatitis B core antibody	SJS	Stephen Johnson Syndrome
HBeAg	Hepatitis B envelope antigen	T1DM	Type 1 diabetes mellitus
HBsAg	Hepatitis B surface antigen	T3	Triiodothyronine
HBV	Hepatitis B virus	T4	Thyroxine
HCC	Hepatocellular cancer	TEN	Toxic Epidermal Necrolysis
HCV	Hepatitis C virus	TMG(s)	Toxicity management guideline(s)
HgA1c	Hemoglobin A1C	TSH	Thyroid stimulating hormone
ICI(s)	Immune checkpoint inhibitor(s)	ULN	Upper limit of normal