A PHASE II TRIAL WITH SAFETY RUN-IN OF NEOADJUVANT THERAPY WITH AN AROMATASE INHIBITOR IN COMBINATION WITH DURVALUMAB (MEDI4736) IN POSTMENOPAUSAL PATIENTS WITH HORMONE-RECEPTOR-POSITIVE BREAST CANCER

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SHORT TITLE: AI AND DURVALUMAB TRIAL IN POSTMENOPAUSAL BREAST CANCER

Protocol Identifying Number: MCC 19803

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LIST OF ABBREVIATIONS

Abbreviation or	Definition/Explanation
AChE	Acetylcholine esterase
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AI	Aromatase inhibitor
ALK	Anaplastic lymphoma kinase
Alkphos	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APF12	Proportion of patients alive and progression free at 12 months from randomization
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration-time curve
$AUC_{0\text{-}28day}$	Area under the plasma drug concentration-time curve from time zero to Day 28 post-dose
AUC_{ss}	Area under the plasma drug concentration-time curve at steady state
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BICR	Blinded Independent Central Review
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BoR	Best objective response
BP	Blood pressure
BUN	Blood urea nitrogen
C	Cycle
C1D1	Cycle 1 Day 1
Ca^{++}	Calcium
CBC	Complete blood count
CD	Cluster of differentiation
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl^{-}	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum plasma concentration

Abbreviation or	Definition/Explanation
$C_{max,ss}$	Maximum plasma concentration at steady state
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CV	Coefficient of variation
CXCL	Chemokine (C-X-C motif) ligand
CYP	Cytochrome P450
DLT	Dose Limiting Toxicity
DoR	Duration of response
D/C	Discontinue
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
e.g.	Exempli gratia (for example)
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
FACS	Fluorescence Activated Cell Sorting
FAS	Full analysis set
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma Glutamyl Transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin

Abbreviation or	Definition/Explanation
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HER-2	Human epidermal receptor-2
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hours
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
i.e.	Id est (that is)
IEC	Independent ethics committee
IFNγ	Interferon-gamma
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
INR	International normalized ratio
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional review board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IU	International unit
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LLQ	Lower limit of quantitation
mAb	Monoclonal antibody
mPEPI	Modified preoperative endocrine prognostic index
M	Metastasis (in pathologic tumor-node-metastasis system)
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid

Abbreviation or	Definition/Explanation
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
N	Node (in pathologic tumor-node-metastasis system)
NCI	National Cancer Institute
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PDx	Pharmacodynamics
PEPI	Preoperative endocrine prognostic index
PFS	Progression Free Survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response; Progesterone receptor
PT	Prothrombin time
PTT	Partial thromboplastin time
Q2W	Every 2 weeks
QnW	Every n weeks where n represents a number
QC	Quality control
QD	Once daily
QTc	QT interval corrected
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RBC	Red blood cell
RNA	Ribonucleic acid
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation or	Definition/Explanation
SAS	Safety analysis set
SD	Standard deviation or stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
sPD-L1	Soluble programmed cell death ligand 1
T	Tumor (in pathologic tumor-node-metastasis system)
$T_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine
T_4	Thyroxine
T_{max}	Time of maximum observed concentration
TID	Three times daily
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
UV	Ultraviolet
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential

All of these abbreviations may or may not be used in protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, I understand it, and I will work, according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the applicable IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

Instructions to the Principal Investigator: SIGN and DATE this signature page and PRINT your name. Return the original, completed and signed, to the HCI Research Compliance Office. Retain a copy in the regulatory binder.

_____ _____

Signature of Principal Investigator Date

_____

Principal Investigator Name (Print)

_____

Name of Institution

STUDY SUMMARY

Title	A phase II trial with safety run-in of neoadjuvant therapy with an aromatase inhibitor in combination with durvalumab (MEDI4736) in postmenopausal patients with hormone-receptor-positive breast cancer.
Short Title	Neoadjuvant study in breast cancer with durvalumab and aromatase inhibitor
Protocol Number	MCC 19803
IND	Exempt
Clinical Phase	Phase II
Design	This is a multi-center, open label, phase II study which will assess the efficacy and safety of an aromatase inhibitor (anastrozole) in combination with durvalumab in patients with hormone-receptor-positive breast cancer.
Study Duration	Enrollment period: 28 months Follow up: Up to 5 years.
Study Center(s)	1. Moffitt Cancer Center; 2. TBD
Objectives	**Primary:** To determine the efficacy of an aromatase inhibitor with durvalumab in achieving the modified Preoperative Endocrine Prognostic Index (mPEPI) Score of 0. **Secondary:** 1. Safety and tolerability 2. Objective clinical response rate (cRR: clinical CR and PR) at up to 24 weeks. 3. Pathologic complete response rate (pCR) at up to 24 weeks (defined as complete absence of invasive cancer in breast and axillary lymph nodes). 4. To determine recurrence free survival. **Exploratory:** 1. To assess immune cell changes (phenotype and functionality) in tumor before, during, and after treatment. 2. To assess cytokine patterns before, during, and after treatment. 3. To assess biomarkers that may correlate with clinical outcome.
Number of Subjects	Up to 46 expected to enroll. Up to 46 expected to be treated. 42 expected to complete treatment (including 6 from safety run-in phase).
Main Eligibility	**Inclusion Criteria:**

Criteria	• Female 18 years of age or older. • ECOG performance status 0 or 1. • Postmenopausal. • Invasive breast cancer; clinical T2-T4c, any N, M0, with goal of definitive surgery after completion of neoadjuvant therapy. • Palpable tumor which size can be measured bidimensionally by tape, ruler or caliper technique, with a largest diameter > 2.0 cm. • Invasive breast cancer is estrogen receptor positive at > 66% or with an Allred score of 6, 7 or 8. • Invasive breast cancer is Human Epidermal Growth Factor Receptor 2 (HER2) negative. • Patients must agree to provide tissue at baseline and at definitive surgery (from the procedure) and undergo a biopsy at baseline and after one cycle of treatment. • Adequate laboratory parameters. **Exclusion Criteria:** • Inflammatory breast cancer. • Excisional biopsy of breast cancer. • Hormone replacement therapy of any type within one week prior to registration. • Surgical axillary staging procedure prior to study entry. • Any treatment for this cancer prior to study entry • History of ipsilateral invasive breast cancer regardless of treatment or ipsilateral ductal carcinoma in situ treated with radiotherapy or endocrine therapy or contralateral invasive breast cancer at any time. • History of another primary malignancy except for malignancy treated with curative intent and with no known active disease ≥ 5 years or adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease or adequately treated carcinoma in situ without evidence of disease e.g., cervical cancer in situ. • Prior use of PD-1, PD-L1 or CTLA-4 inhibitors • Active or prior documented autoimmune or inflammatory disorders within the past 5 years. • Current or prior use of immunosuppressive medication within 14 days before the first dose of study drug. • Clinically significant cardiovascular disease. • Currently active systemic infection. • History of HIV infection or chronic hepatitis B or C. • History of previous clinical diagnosis of tuberculosis, uncontrolled seizures, organ transplant, primary immunodeficiency, interstitial lung disease (ILD)/pneumonitis. • Receipt of live attenuated vaccination within 30 days of first

	dose of study drug. • Weighing 30 kg or less.
Study Product, Dose, Route, Regimen	Durvalumab, 1500 mg (equivalent to 20 mg/kg) IV Q4W, on Day 1 of each 28-day cycle x 6 cycles (6 months) Anastrozole 1 mg PO QD [in the post DLT period, as per standard of care, it is OK to switch to another AI (letrozole 2.5 mg or exemestane 25 mg PO daily) for intolerance such as hot flash or joint ache that is attributed to AI] .
Duration of administration	Six months prior to definitive surgery
Statistical Methodology	**Safety Analysis:** will include all subjects who received at least 1 dose of AI or durvalumab. **Efficacy Analysis:** will include all subjects who received at least one dose of AI and one dose of durvalumab.

1 STUDY OBJECTIVES AND ENDPOINTS

1.1 Study Objectives

1.1.1 Primary Objective

- To evaluate the efficacy of an aromatase inhibitor with durvalumab

1.1.2 Secondary Objectives

- To evaluate safety and tolerability of the combination of an aromatase inhibitor and durvalumab
- To evaluate objective clinical response rate
- To evaluate pathologic complete response rate (pCR)
- To evaluate recurrence free survival.

1.1.3 Exploratory Objective and Endpoints

- To assess immune cell changes (phenotype and/or functionality) in tumor before, during and after treatment.
- To assess cytokine patterns before, during and after treatment.
- To evaluate biomarkers that may correlate with clinical outcome.

1.2 Study Endpoints

1.2.1 Primary Endpoints

- Rate of modified Preoperative Endocrine Prognostic Index (mPEPI) Score of 0.

1.2.2 Secondary Endpoints

- Type, incidence, severity, attribution and timing of adverse events.
- Objective clinical response rate (cRR = clinical CR + PR) at up to 24 weeks.
- Pathologic complete response rate (pCR) at time of definitive surgery (defined as complete absence of invasive cancer in breast and axillary lymph nodes).
- Recurrence free survival defined as the time between first treatment and disease recurrence.

1.2.3 Exploratory Objective and Endpoints

- Change in immune cells' phenotype and/or functionality before, during and after treatment.
- Cytokine patterns before, during and after treatment.
- Biomarkers that may correlate with clinical outcome.

2 BACKGROUND

2.1 Disease Background

2.1.1 Hormone-Receptor-Positive Breast Cancer

In the U.S., 255,180 new cases of invasive breast cancer and 41,070 deaths due to breast cancer were expected in 2017 (1). 70% - 80% of breast cancer are hormone-receptor (ER) positive disease (2). Even though ER-positive breast cancer is considered to have a better prognosis than triple-negative or human epidermal growth factor receptor 2-(HER2) positive disease, late cancer recurrence is a major concern.

Data from the International Breast Cancer Study Groups I-V involving 4,105 patients treated from 1978 to 1985 showed that the recurrence rate was higher for ER-negative breast cancer during the first five years, but higher in ER-positive breast cancer from year 5 to 25. The cumulative incidence of recurrence for all sites (local, contralateral, regional, and distant) at year 5, 10, 15, 20, and 25 was 39.4%, 53.2%, 59%, 63.4%, and 64.9%, respectively for ER-positive breast cancer versus 44.3%, 52.5%, 55.3%, 57.7%, and 59.9%, respectively for ER-negative breast cancer.

Similarly, the cumulative distant recurrence rate was higher for ER-negative breast cancer compared with ER-positive breast (27.1% versus 23.4%) for the first five year. However, ER-positive breast cancer had a higher cumulative distant recurrence beyond year 5, 31.9% versus 31.8% at year 10, 35% versus 33.4% at year 15, 37.4% versus 34.1% at year 20, and 38.3% versus 35.3% (3).

A recent meta-analysis looked at 62,923 patients with ER-positive breast cancer enrolled in 88 clinical trials who had no recurrence after 5 years of adjuvant endocrine therapy. Even in this group of patients who were supposed to have a good prognosis having survived the first 5 years cancer free, breast cancer recurrences were found to occur throughout the follow up period over the next 15 years. Even for small tumor (T1, $\leq$ 2 cm), the risk of distant recurrence was substantial, 13%, 20%, and 34% for node negative (N0), 1 to 3 nodes positive (N1), and 4 to 9 nodes positive (N2), respectively. For medium size tumor (T2, >2 cm to $\leq$ 5 cm), the risk for distant recurrence was 19%,

26%, and 41% for node negative (N0), 1 to 3 nodes positive (N1), and 4 to 9 nodes positive (N2), respectively (4).

The meta-analysis only studied T1 and T2 disease. Given the risk of recurrence being strongly correlated with the original TN stages (4), this means that T3 or T4 disease with or without positive nodes (part of the patient population in our proposed study) will have even a much higher rate of distant recurrence.

2.1.2 Neoadjuvant Endocrine Therapy Breast Cancer

Endocrine therapy has been used extensively for the treatment of breast cancer in the adjuvant and metastatic setting. It has also shown similar benefit to chemotherapy in the neoadjuvant setting but with significantly lower toxicity, and endocrine therapy with an aromatase inhibitor (AI) is now considered a standard of care for the neoadjuvant treatment of postmenopausal women with ER+ breast cancer. In the ACOSOG Z1031 trial, the clinical response rate for anastrozole, letrozole, and exemestane was 69.1%, 74.8%, and 62.9%, respectively. Severe toxicity was observed in less than 5% of patients. The most common grade 2 toxicity was hot flashes (5).

The Preoperative Endocrine Prognostic Index (PEPI) score was developed using results of the P024 trial to assess the risk of relapse based on pathologic tumor size, lymph node status, Ki67 level, and ER status of surgery specimen post neoadjuvant endocrine therapy (6). With a median follow up of 61.2 months, patients with confirmed baseline ER+ clinical stage 2 and 3 tumors that were down-staged to stage 1 or 0 at surgery had 100% recurrence free survival (RFS) compared with higher stages ($P < 0.001$). Multivariable testing of post-treatment tumor characteristics revealed that pathological tumor size, node status, Ki67 level, and ER status were independently associated with both RFS and breast cancer specific survival (BCSS). The PEPI model based on these factors predicted RFS in the IMPACT trial ($P = 0.002$).

In the ALTERNATE study using fulvestrant and/or anastrozole in treating postmenopausal patients with stage II-III breast cancer undergoing definitive surgery (NCT01953588, sponsored by the Alliance for Clinical Trials in Oncology and the NCI, 2820 patients), one of the primary objectives is to evaluate whether patients who achieve a modified PEPI (mPEPI) score of 0, defined by pathologic tumor size $\leq$ 5 cm, pathologic N0, Ki67 $\leq$ 2.7%, at surgery post 6 months of neoadjuvant endocrine therapy will have excellent long term outcome, for whom chemotherapy is unnecessary (7).

In the combined analysis of the P024 and POL trials, no relapses were observed during a median follow up of 5 years in patients with PEPI 0 after neoadjuvant endocrine treatment (7).

2.2 Immunotherapies

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 (8).

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 (9). It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) (10). 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 (11). Importantly, PD-L1 is commonly over-expressed on tumor cells or on non-transformed cells in the tumor microenvironment (12). 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 (13-18) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (19-21). In addition, high mutational burden (e.g., in bladder carcinoma (22) may contribute to the responses seen with immune therapy).

Pre-clinical data have now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as programmed death ligand 1 (PD-L1) has promising clinical activity. Nivolumab and pembrolizumab, two anti–PD-1 agents, and atezolizumab, avelumab and durvalumab, three anti–PD-L1 agents have been granted approvals by the US FDA for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer and urothelial carcinoma. In addition, there are data from agents in the anti–PD-1/PD-L1class showing clinical activity in a wide range of tumor types.

2.2.1 Checkpoint inhibitors in breast cancer

Checkpoint inhibitors have not been approved in the treatment of breast cancer. However, there are several clinical trials that are either completed or on going that looked at checkpoint inhibitors either as a single agent or in combination with other drugs such as chemotherapy or endocrine therapy.

In KeyNote-012 phase Ib study, 65 patients with refractory metastatic triple negative breast cancer whose tumor expressed at least 1% PD-L1 were treated with single agent anti-PD1 monoclonal antibody (mAb) pembrolizumab. The overall response rate (ORR) was 18.5%. The median overall survival was 11.3 months which surpassed expectation of what would have been achieved with chemotherapy (23).

In the Enhance-1 phase I study (KeyNote-150), pembrolizumab in combination with eribulin mesylate in triple negative patients showed an ORR for first line therapy of 41%, and 27.3% for second or third line therapy. Responses were seen regardless of PD-L1 status (24)

In a phase Ib study combining the anti-PD-L1 mAb atezolimumab with nab-paclitaxel chemotherapy in patients with metastatic triple negative breast cancer, there was no dose limiting toxicity (DLT) or treatment-related death. The confirmed ORR for all patients was 42%, with an ORR for first line

treatment of 67%. Responses occurred in both PD-L1 positive and PD-L1 negative patients (25). In a follow up phase III Impassion130 study enrolling 902 patients with triple negative breast cancer regardless of PD-L1 expression, Roche announced in July 2018 that atezolimumab plus nab-paclitaxel had met its co-primary endpoint of significant improvement in progression free survival over that of nab-paclitaxel alone with no new safety issues (26). This data will be presented at San Antonio Breast cancer Conference in December 2018.

KeyNote-028 phase I study enrolled 25 patients with refractory ER-positive, HER2-negative breast cancer, with a median prior number of therapies of 9 (range 3 to 15). The ORR was 12%. The clinical benefit rate was 20%. Median duration of response was 12 months. Treatment was well tolerated with toxicities primarily grade 1 and 2 (27).

Currently there are multiple ongoing clinical trials combining a checkpoint inhibitor with chemotherapy or endocrine therapy to treat breast cancer, including ER-positive, HER-2 negative breast cancer. In the neoadjuvant ISPY2 trial which Moffitt is a study site, pembrolizumab plus paclitaxel or the anti-PD-L1 mAb durvalumab plus olaparib and paclitaxel are two of the neoadjuvant treatment arms for ER-negative or ER-positive, HER2-negative breast cancer (NCT01042379). In a current phase II study sponsored by City of Hope Medical Center in collaboration with the National Cancer Institute, pembrolizumab is given together with an aromatase inhibitor for the treatment of metastatic ER-positive HER2-negative breast cancer (NCT02648477).

2.2.2 Durvalumab

The non-clinical and clinical experience is fully described in the most current version of the durvalumab Investigator's Brochure.

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document). The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ (28). *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (28). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 1.5.2.1 and Section 6.5 Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

2.3 Research hypothesis

Endocrine therapy has been used extensively in the treatment of ER+ breast cancer. There are differences in immune modulation among different classes of endocrine agents. Tamoxifen has been shown to shift immune response from a Th1 to a Th2 pathway (29), which is undesirable in immunotherapy against cancer.

Anastrozole has been shown to shift immunity in the other direction, i.e., from a Th2 to a Th1 pathway, by increasing IFNγ and IL-12 and by decreasing IL-4 and IL-10. In addition, anastrozole has also been shown to decrease regulatory T cell numbers and function (30). Increased gene expression relating to inflammatory changes has been reported with anastrozole (31).

Letrozole has been shown to enhance immune response to a MUC-1 cancer vaccine in animal model (32) and to decrease regulatory T cells in tumors of patients with breast cancer (33). Mean serum levels of IFNγ were reduced with thymosin-α treatment in patients on aromatase inhibitor who experienced arthralgia (34), indicating immunomodulation by aromatase inhibitors.

IFNγ is a potent inducer of PD-L1 expression in tumor cells (35, 36). Therefore, it is possible that aromatase inhibitors upregulate PD-L1 expression in tumor cells through induction of expression of inflammatory cytokines such as IFNγ. PD-L1 expression in breast cancer has been shown to be associated with high Ki67 expression (37).

Therefore, we hypothesize that combining an aromatase inhibitor with the anti-PD-L1 durvalumab may lead to improved clinical outcome, particularly the mPEPI score, compared to outcomes with each drug given as a single agent.

2.4 Rationale for conducting this study

As stated in section 2.1.2, AI treatment is associated with high clinical response rate in the neoadjuvant treatment of breast cancer; in addition, AI treatment has also been shown to have immunomodulatory activity. However, breast cancer routinely develops resistance to endocrine therapy, leading to recurrence and progression of disease. Therefore, a combination of an AI and immunotherapies such as checkpoint inhibitors may yield good responses that are durable.

As an antibody that blocks the interaction between PD-L1 and its receptors, durvalumab may relieve PD-L1-dependent immunosuppressive effects and, therefore, enhance the cytotoxic activity of anti-tumor T-cells. This hypothesis is supported by emerging clinical data from other mAbs targeting the PD-L1/PD-1 pathway, which provide early evidence of clinical activity and a manageable safety profile. Responses have been observed in patients with PD-L1-positive tumors and patients with PD-L1-negative tumors. In addition, durvalumab monotherapy has shown durable responses in NSCLC in Study 1108 (see section 2.2.1).

2.5 Rationale for dose selection

2.5.1 Aromatase inhibitor

The standard dose for anastrozole is 1 mg orally (PO) daily.

After the dose-limiting toxicity (DLT) period in the safety run-in stage, as per standard of care, switching AI is allowed for intolerance that is attributed to the AI. The ACOSOG Z1031 study demonstrated no significant difference among these AIs in terms of efficacy and side effect profiles (5). Additionally, the Rheumatologic Evaluation of Adjuvant Letrozole in Postmenopausal Women

with Breast Cancer (REAL) study showed that women who experienced ≥ grade 2 arthralgias/myalgias while receiving anastrozole who switched to letrozole developed significantly less arthralgias/myalgias and had improved quality of life compared with baseline (38).

Our institutional standard of care (SOC) guidelines allow switching from one AI to another and we have observed patients who experienced side effects with anastrozole but tolerated letrozole with minimal or no issues, and vice versa (people who had side effects with letrozole but did well on anastrozole).

The standard doses for letrozole and exemestane are 2.5 mg and 25 mg PO daily, respectively.

2.5.1.1 Durvalumab monotherapy dose rationale

A durvalumab dose of 20 mg/kg Q4W 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).

PK/Pharmacodynamic data

Based on available 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 21 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 (39). 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 AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median $C_{trough,ss}$ 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.

Fixed dosing for durvalumab

A population PK model was developed for durvalumab using monotherapy data from a Phase 1 study (study 1108; N = 292; doses = 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors).

Population PK analysis indicated only minor impact of body weight 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 patients were simulated using body weight distribution of 40–120 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.

Similar findings have been reported by others (40-43). 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. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters.

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 weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

Fixed dosing of durvalumab is recommended only for subjects with > 30kg body weight due to endotoxin exposure. Patients with a body weight less than or equal to 30 kg will not receive any further durvalumab.

3 DRUG INFORMATION

3.1 Potential risks

3.1.1 Commercial drugs

The aromatase inhibitors anastrozole, letrozole or exemestane are standard of care drugs and must be obtained from commercial sources. Common side effects of each drug are described in Tables 1 through 3 below.

Table 1. Anastrozole - adverse reactions occurring with an incidence of at least 5% in either treatment group during treatment, or within 14 days of the end of treatment in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial (this table is from anastrozole package insert).

Body system and adverse reactions	**Anastrozole 1 mg** (n = 3092)	**Tamoxifen 20 mg** (n = 3094)
Body as a whole		
Asthenia	575 (19)	544 (18)
Pain	533(17)	485 (16)
Back pain	321 (10)	309 (10)
Headache	314 (10)	249 (8)
Abdominal pain	271 (9)	276 (9)
Infection	285 (9)	276 (9)
Accidental injury	311 (10)	303 (10)

Flu syndrome	175 (6)	195 (6)
Chest pain	200 (7)	150 (5)
Neoplasm	162 (5)	144 (5)
Cyst	138 (5)	162 (5)
Cardiovascular		
Vasodilatation	1104 (36)	1264 (41)
Hypertension	402 (13)	349 (11)
Digestive		
Nausea	343 (11)	335 (11)
Constipation	249 (8)	252 (8)
Diarrhea	265 (9)	216 (7)
Dyspepsia	206 (7)	169 (6)
Gastrointestinal disorder	210 (7)	158 (5)
Hemic and lymphatic		
Lymphedema	304 (10)	341 (11)
Anemia	113 (4)	159 (5)
Metabolic and nutritional		
Peripheral edema	311 (10)	343 (11)
Weight gain	285 (9)	274 (9)
Hypercholesterolemia	278 (9)	108 (3.5)
Musculoskeletal		
Arthritis	512 (17)	445 (14)
Arthralgia	467 (15)	344 (11)
Osteoporosis	325 (11)	226 (7)
Fracture	315(10)	209 (7)
Bone pain	201 (7)	185 (6)
Arthrosis	207 (7)	156 (5)
Joint Disorder	184 (6)	160 (5)
Myalgia	179 (6)	160 (5)
Nervous system		
Depression	413 (13)	382 (12)
Insomnia	309 (10)	281 (9)
Dizziness	236 (8)	234 (8)
Anxiety	195 (6)	180 (6)
Paresthesia	215 (7)	145 (5)
Respiratory		
Pharyngitis	443 (14)	422 (14)
Cough increased	261 (8)	287 (9)
Dyspnea	234 (8)	237 (8)
Sinusitis	184 (6)	159 (5)
Bronchitis	167 (5)	153 (5)
Skin and appendages		
Rash	333 (11)	387 (13)

Sweating	145 (5)	177 (6)
Special Senses		
Cataract Specified	182 (6)	213 (7)
Urogenital		
Leukorrhea	86 (3)	286 (9)
Urinary tract infection	244 (8)	313(10)
Breast pain	251 (8)	169 (6)
Breast Neoplasm	164 (5)	139 (5)
Vulvovaginitis	194 (6)	150 (5)
Vaginal Hemorrhage [1]	122 (4)	180 (6)
Vaginitis	125 (4)	158 (5)

[1] Vaginal Hemorrhage without further diagnosis.

Note: The combination arm was discontinued due to lack of efficacy benefit at 33 months of follow-up.

Table 2. Letrozole - patients with adverse reactions (CTC Grades 1-4, irrespective of relationship to study drug) in the adjuvant study - monotherapy arms analysis (median follow-up 73 months; median treatment 60 months). This table is from letrozole package insert.

Adverse reaction	**Grades 1-4**		**Grades 3-4**	
	Letrozole n = 2448 n (%)	**Tamoxifen n = 2447 n (%)**	**Letrozole n = 2448 n (%)**	**Tamoxifen n = 2447 n (%)**
Pts with any adverse event	2310 (94.4)	2214 (90.5)	635 (25.9)	604 (24.7)
Hypercholesterolemia	1280 (52.3)	700 (28.6)	11 (0.4)	6 (0.2)
Hot Flashes/Flushes	821 (33.5)	929 (38.0)	0 -	0 -
Arthralgia/Arthritis	618 (25.2)	501 (20.4)	85 (3.5)	50 (2.0)
Night Sweats	357 (14.6)	426 (17.4)	0 -	0 -
Bone Fractures[2]	338 (13.8)	257 (10.5)	- -	- -
Weight Increase	317 (12.9)	378 (15.4)	27 (1.1)	39 (1.6)
Nausea	283 (11.6)	277 (11.3)	6 (0.2)	9 (0.4)
Bone Fractures[1]	247 (10.1)	174 (7.1)	- -	- -
Fatigue (Lethargy, Malaise, Asthenia)	235 (9.6)	250 (10.2)	6 (0.2)	7 (0.3)
Myalgia	217 (8.9)	212 (8.7)	18 (0.7)	14 (0.6)
Edema	164 (6.7)	160 (6.5)	3 (0.1)	1 (< 0.1)
Weight Decrease	140 (5.7)	129 (5.3)	8 (0.3)	5 (0.2)
Vaginal Bleeding	128 (5.2)	320 (13.1)	1 (< 0.1)	8 (0.3)
Back Pain	125 (5.1)	136 (5.6)	7 (0.3)	11 (0.4)
Osteoporosis NOS	124 (5.1)	66 (2.7)	10 (0.4)	5 (0.2)
Bone pain	123 (5.0)	109 (4.5)	6 (0.2)	4 (0.2)
Depression	119 (4.9)	114 (4.7)	16 (0.7)	14 (0.6)
Vaginal Irritation	111 (4.5)	77 (3.1)	2 (< 0.1)	2 (< 0.1)

Headache	105 (4.3)	94 (3.8)	9 (0.4)	5 (0.2)
Pain in extremity	103 (4.2)	79 (3.2)	6 (0.2)	4 (0.2)
Osteopenia	87 (3.6)	74 (3.0)	0 -	2 (< 0.1)
Dizziness/Light-Headedness	84 (3.4)	84 (3.4)	1 (< 0.1)	6 (0.2)
Alopecia	83 (3.4)	84 (3.4)	0 -	0 -
Vomiting	80 (3.3)	80 (3.3)	3 (0.1)	5 (0.2)
Cataract	49 (2.0)	54 (2.2)	16 (0.7)	17 (0.7)
Constipation	49 (2.0)	71 (2.9)	3 (0.1)	1 (< 0.1)
Breast pain	37 (1.5)	43 (1.8)	1 (< 0.1)	0 -
Anorexia	20 (0.8)	20 (0.8)	1 (< 0.1)	1 (< 0.1)
Endometrial Hyperplasia/ Cancer[2, 3]	11/1909 (0.6)	70/1943 (3.6)	-	-
Endometrial Proliferation Disorders	10 (0.3)	71 (1.8)	0 -	14 (0.6)
Endometrial Hyperplasia/ Cancer[1, 3]	6/1909 (0.3)	57/1943 (2.9)	-	-
Other Endometrial Disorders	2 (< 0.1)	3 (0.1)	0	0
Myocardial Infarction[1]	24 (1.0)	12 (0.5)	-	-
Myocardial Infarction[2]	37 (1.5)	25 (1.0)	-	-
Myocardial Ischemia	6 (0.2)	9 (0.4)	-	-
Cerebrovascular Accident[1]	52 (2.1)	46 (1.9)	-	-
Cerebrovascular Accident[2]	70 (2.9)	63 (2.6)	-	-
Angina[1]	26 (1.1)	24 (1.0)	-	-
Angina[2]	32 (1.3)	31 (1.3)	-	-
Thromboembolic Event[1]	51 (2.1)	89 (3.6)	-	-
Thromboembolic Event[2]	71 (2.9)	111 (4.5)	-	-
Other Cardiovascular[1]	260 (10.6)	256 (10.5)	-	-
Other Cardiovascular[2]	312 (12.7)	337 (13.8)	-	-
Second Malignancies[1]	53 (2.2)	78 (3.2)	-	-
Second Malignancies[2]	102 (4.2)	119 (4.9)	-	-

[1] During study treatment, based on Safety Monotherapy population.
[2] Any time after randomization, including post treatment follow-up.
[3] Excluding women who had undergone hysterectomy before study entry.

Note: Cardiovascular (including cerebrovascular and thromboembolic), skeletal and urogenital/endometrial events and second malignancies were collected life-long. All of these events were assumed to be of CTC Grade 3 to 5 and were not individually graded.

Table 3. Exemestane - incidence (%) of adverse events of all grades and illnesses occurring in (≥ 5%) of patients in any treatment group in the Intergoup Exemestane Study (IES) in postmenopausal women with early breast cancer. This table is from exemestane package insert.

Body system and adverse event[1]	**% of patients**	
	Exemestane 25 mg daily (n = 2252)	**Tamoxifen 20 mg daily[2] (n = 2280)**
Eye		

Visual disturbances[3]	5	3.8
Gastrointestinal		
Nausea[3]	8.5	8.7
General Disorders		
Fatigue[3]	16.1	14.7
Musculoskeletal		
Arthralgia	14.6	8.6
Pain in limb	9.0	6.4
Back pain	8.6	7.2
Osteoarthritis	5.9	4.5
Nervous System		
Headache[3]	13.1	10.8
Dizziness[3]	9.7	8.4
Psychiatric		
Insomnia[3]	12.4	8.9
Depression	6.2	5.6
Skin & Subcutaneous Tissue		
Increased sweating[3]	11.8	10.4
Vascular		
Hot flushes[3]	21.2	19.9
Hypertension	9.8	8.4

[1] Graded according to Common Toxicity Criteria;
[2] 75 patients received tamoxifen 30 mg daily;
[3] Event actively sought.

Please refer to the current Food and Drug Administration (FDA)-approved package inserts provided with the medications or the Physicians' Desk Reference for additional information about possible side effects and instructions for preparation, handling, and storage of the drugs.

3.1.2 Durvalumab monotherapy

Risks with durvalumab include, but are not limited to, diarrhea/colitis and intestinal perforation, pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus, hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions and infections/serious infections.

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

Further information on these risks can be found in the current version of the durvalumab IB.

In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% 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% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and

approximately 6% of patients experienced an 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 (Appendix 1).

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

4 STUDY DESIGN

4.1 Description

This is a multi-center, open label phase II with safety run-in study. This study will assess the efficacy and safety of an aromatase inhibitor (anastrozole) in combination with durvalumab in patients with hormone-receptor-positive breast cancer. The objectives are to obtain data on the clinical efficacy and to assess the safety of the drug combination.

The study will test a fixed dose of durvalumab in combination with an AI. Initially, six patients will be enrolled in the safety run-in stage. If $\leq$1/6 patients have a DLT, then the expansion stage will be open for enrollment. If $\geq$2/6 patients have a DLT, we will amend the protocol.

Anastrozole 1 mg daily will be taken orally (PO) starting on Day 1 of each cycle for 6 months prior to definitive surgery. After the first 6 months, the patients will continue taking the AI at the discretion of the treating physician as per standard of care.
It is acceptable to switch to another AI (letrozole 2.5 mg or exemestane 25 PO mg daily) for intolerance such as hot flash or joint ache attributable to the AI). In the safety run-in phase, switching to another AI is allowed only after the post DLT period.

Table 4. Dosage for durvalumab and AI combination.

Durvalumab (IV)	AI (PO)
1500 mg Q4W on Day 1 of each 28-day cycles for 6 cycles	Anastrozole 1 mg (or letrozole 2.5 mg or exemestane 25 mg, if intolerance of anastrozole) for 6 months

4.1.1 Dose expansion phase

All patients will also receive a daily dose of the aromatase inhibitor anastrozole (1 mg PO). Patients will be allowed to switch to another AI for toxicity reasons as described in section 2.5.1 at any time their treating physicians deems it necessary.

4.2 Dose Limiting Toxicity

Dose-limiting toxicities (DLTs) will be evaluated during the safety run-in phase of the trial. The period for evaluating DLTs will be the first cycle of treatment (from the time of first administration of durvalumab until the clinic evaluation prior to C2D1 dosing). Subjects who do not remain on the study up to this time for reasons other than DLT will be replaced with another subject. Grading of

DLTs will follow the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

A DLT will be defined as any Grade 3 or higher toxicity that occurs during the DLT evaluation period and meets the criteria below. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. The following will be DLTs:

- Any Grade 4 irAE (as defined in section 15.4.4 and 15.4.5).
- Any Grade ≥ 3 colitis.
- Any Grade ≥ 3 noninfectious pneumonitis irrespective of duration.
- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care.
- Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days of onset despite optimal medical management including systemic corticosteroids or does not downgrade to Grade ≤ 1 or baseline within 14 days.
- Liver transaminase elevation > 8 × ULN or total bilirubin > 5 × ULN.
- Grade 3 or 4 febrile neutropenia
- Any treatment interruption greater than 2 weeks due to an AE.
- Any ≥ Grade 3 non-irAE, except for the exclusions listed below.

The definition excludes the following conditions:

- Grade 3 fatigue lasting ≤ 7 days.
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic.
- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.).
- Concurrent vitiligo or alopecia of any AE grade.
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management.
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility.
- Grade 3 or 4 lymphopenia.
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days.
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days.

Immune-related AEs are defined as AEs of an immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

4.3 Number of Patients

Safety run-in phase: 6 patients

Expansion phase: A total of 42 evaluable patients are required, when considering a rate of non-evaluability of 10%, a total of 46 patients are expected to enroll in the study (the 6 patients in the safety run-in phase are included in this total).

4.4 Number of Study Centers

The study will be conducted at two centers.

4.5 Duration

The total enrollment period for the study will be 28 months. Follow-up will be required for up to 5 years.

4.6 Withdrawal of Subjects from Study Treatment and/or Study

4.6.1 Permanent discontinuation of investigational product

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

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

2. Withdrawal of consent or lost to follow-up

3. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing

4. Patient is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk

5. Any AE that meets criteria for discontinuation as defined in Section 10.3 and Appendix 1.

6. Dose-limiting toxicity (as defined in section 4.2)

7. Grade ≥3 infusion reaction

8. Patient noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits

9. Initiation of alternative anticancer therapy including another investigational agent

10. Confirmation of PD and investigator determination that the patient is no longer benefiting from treatment with durvalumab

11. Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section 15.4 and Appendix 1, including the collection of any protocol-

specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. All subjects will be followed for recurrence free survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

4.6.2 Withdrawal of consent

Patients are free to withdraw from the study at any time (from investigational product and assessments) without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further investigational product 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 (e.g., survival contact telephone calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples

4.6.3 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated samples, the Principal Investigator will ensure that any stored samples are disposed of or destroyed, the action is documented, and the subject is notified of the samples' disposal. As collection of the biological samples is an integral part of the study, the subject will also be withdrawn from further study participation.

4.7 Replacement of subjects

Patients enrolled in the safety run-in phase of the study may be replaced if they are not evaluable for DLT (i.e., patients did not receive study treatment or withdrawn from the study for reasons other than drug-related toxicity) will need to be replaced to provide adequate evaluation of safety at the tested dose level.

Patients enrolled in the safety run-in phase who withdraw from the study after completing the first treatment cycle (DLT period) will not need to be replaced on the study.

Patients enrolled in the expansion phase of the study will not be replaced.

5 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with signature in the patient research chart.

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances will there be exceptions to this rule.

Patient No. _____

Patient's Initials: (L,F,M) _____

5.1 Inclusion Criteria

Yes/No (Response of "no" = patient ineligible)

_____ 5.1.1 Able to provide a written informed consent and any locally-required authorization (e.g., HIPAA in the USA) prior to performing any protocol-related procedures, including screening evaluations.

_____ 5.1.2 Female age ≥ 18 years at time of study.

_____ 5.1.3 Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

_____ 5.1.4 Postmenopausal, defined as meeting at least 1 of the following criteria:

- Age ≥ 60
- Prior bilateral oophorectomy
- Age < 60 with a uterus AND amenorrhea for at least the past 12 months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression)
- Age < 60 without a uterus AND follicular stimulating hormone (FSH) and estradiol in the postmenopausal range per local normal range

_____ 5.1.5 Clinical T2-T4c, any N, M0 by AJCC 8th edition, with the goal being definitive surgery after completion of neoadjuvant therapy.

- The tumor is palpable and its size can be measured bidimensionally by tape, ruler or caliper technique
- The largest tumor diameter is > 2.0 cm

_____ 5.1.6 Pathologic confirmation of invasive breast cancer that is estrogen receptor (ER) positive with an Allred score of 6, 7 or 8. If an Allred Score is not reported on the diagnostic pathology report, ER positivity in > 66% cells is eligible. If ER positivity is ≤ 66%, the staining intensity (weak, intermediate, strong) is needed to calculate the Allred Score to determine eligibility.

_____ 5.1.7 Invasive breast cancer is Human Epidermal Growth Factor Receptor 2 (HER2) negative defined as 0 or 1+ by immunohistochemistry (IHC) or with an in situ hybridization (ISH) ratio (HER2 gene copy/chromosome 17) < 2.

_____ 5.1.8 Documentation of mammogram and ultrasound [including ductal carcinoma in situ (DCIS) and invasive cancer] of the diseased breast performed within 60 days prior to enrollment. Mammogram for the unaffected contralateral breast is required within 12 months prior to enrollment.

_____ 5.1.9 Adequate organ and marrow function as defined below, laboratory values obtained ≤ 14 days prior to enrollment:

- Hemoglobin ≥ 9.0 g/dL
- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1500 per mm^3)
- Platelet count ≥ 100 x 10^9/L (≥ 100,000 per mm^3)
- Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects 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) ≤ 2.5 x institutional upper limit of normal.
- Serum creatinine clearance > 40 mL/min by the Cockcroft-Gault formula (1976) or by 24-hour urine collection for determination of creatinine clearance

_____ 5.1.10 Subjects must be willing to undergo a research biopsy at baseline and after one cycle of treatment and to provide tissue obtained at surgery for biomarker and correlative studies.

_____ 5.1.11 Subjects must be 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.

_____ 5.1.12 If taking herbal or natural remedies that may have immune modulatory effects, subjects must be willing to discontinue it prior to first dose of durvalumab.

_____ 5.1.13 Body weight > 30 kg.

5.2 Exclusion Criteria

Yes/No (Response of "yes" = patient ineligible)

_____ 5.2.1 Participation in another clinical study with an investigational product during the last 4 weeks.

_____ 5.2.2 Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study

_____ 5.2.3 Inflammatory breast cancer defined as clinically significant erythema of the breast and/or documented dermal lymphatic invasion (not direct skin invasion by tumor or peau d'orange without erythema).

_____ 5.2.4 An excisional biopsy of this breast cancer.

_____ 5.2.5 Hormone replacement therapy of any type, megestrol acetate, or raloxifene within one week prior to registration.

_____ 5.2.6 Surgical axillary staging procedure prior to study entry. Note: Fine needle aspiration (FNA) or core needle biopsy of axillary node is permitted.

_____ 5.2.7 Treatment for this cancer including surgery, radiation therapy, chemotherapy, biotherapy, hormonal therapy or investigational agent prior to study entry.

_____ 5.2.8 Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab

_____ 5.2.9 History of another primary malignancy except for malignancy treated with curative intent and with no known active disease ≥ 5 years or adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease or adequately treated carcinoma in situ without evidence of disease e.g., cervical cancer in situ.

_____ 5.2.10 History of ipsilateral invasive breast cancer regardless of treatment or ipsilateral ductal carcinoma in situ (DCIS) treated with radiotherapy or endocrine therapy or contralateral invasive breast cancer at any time.

_____ 5.2.11 Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab, with the exceptions of intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection); systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid; or steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

_____ 5.2.12 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

_____ 5.2.13 History of primary immunodeficiency.

_____ 5.2.14 History of allogeneic organ transplant.

_____ 5.2.15 Known allergy or history of hypersensitivity to durvalumab, or any excipient.

_____ 5.2.16 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses, , or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.

_____ 5.2.17 Known 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**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). 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. Note: This is applied only to patients with known infection. Screening tests for TB, hepatitis B and C, or HIV are not required.

_____ 5.2.18 Receipt of live attenuated vaccination within 30 days prior to receiving durvalumab. Note: Patients, if enrolled, should not receive live vaccine while receiving durvalumab and up to 30 days after the last dose of durvalumab.

_____ 5.2.19 Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.

_____ 5.2.20 Subjects with uncontrolled seizures.

_____ 5.2.21 Patients with multi-centric breast cancer (defined as more than one lesion is invasive breast cancer in the same breast separated by ≥ 2 cm of normal breast tissue

_____ 5.2.22 Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of investigational product.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

_____	_____	_____
Investigator Signature	**Date**	**Time**

6 TREATMENT PLAN

6.1 Administration Schedule

6.1.1 Aromatase inhibitors

Anastrozole will be administered at a fixed dose of 1 mg PO once daily (QD) regardless of the subject's weight.

On cycle 1 day 1 (C1D1), patients are to take anastrozole prior to the infusion of durvalumab. Patients will then be encouraged to take their daily dose of anastrozole at approximately the same time each day at their convenience. Doses must be taken at least 18 hours apart.

If patients need to switch to another AI for intolerance reasons (such as hot flash or joint ache) in the post DLT period, they will be given letrozole (2.5 mg PO QD) or exemestane (25 mg PO QD).

6.1.2 Durvalumab

Durvalumab will be administered as follows:

> Durvalumab, 1500 mg via IV infusion Q4W (equivalent to 20 mg/kg Q4W) on Day1 of each 28-day cycle for 6 cycles (6 doses – 6 months).

6.2 How Supplied, Stored, Packaged and Labeled

6.2.1 Commercial products

The aromatase inhibitors anastrozole, letrozole or exemestane are standard of care drugs and must be obtained from commercial sources. Please refer to the current FDA-approved package inserts provided with the medications or the Physicians' Desk Reference for instructions for preparation, handling, and storage.

6.2.2 Investigational drugs

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab (MEDI4736) to the investigator as a 500-mg vial solution for infusion after dilution. Durvalumab will be supplied to the study as a commercial product.

6.2.2.1 Formulation/packaging/storage

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 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. The nominal fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.

6.3 Preparation and Administration

The dose of durvalumab (MEDI4736) for administration must be prepared by the Investigator or site designated investigational product (IP) manager using aseptic technique.

Fixed doses will be used based on an average body weight of 75 kg:

- Durvalumab: 1500 mg Q4W (equivalent to 20 mg/kg Q4W).

Total time from needle puncture of the vials to start of administration should not exceed 24 hours at 2 °C - 8 °C (36°F to 46°F) or 4 hours at room temperature.

Infusion solutions must be allowed to equilibrate to room temperature prior to beginning administration.

A dose of 1500mg (for patients >30kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 30.0 mL of durvalumab (MEDI4736) (ie, 1500mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time is 1 hour. In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

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

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

6.4 Monitoring of dose administration

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. The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 4 hours at room temperature, with maximum total time at room temperature not exceeding 4 hours (otherwise requires new infusion preparation). For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines in **Error! Reference source not found.**appendix 1.

A 1 hour observation period is required after the first infusion of durvalumab. If no clinically significant infusion reactions are observed during or after the first two cycles, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab infusion).

Instructions for the management of infusion-related reactions or allergic reactions can be found in section 15.4.4 and Appendix 1.

6.5 Accountability and Compliance

The investigator will not supply investigational drug to any patient not enrolled in the study, or to any physicians or scientists except those designated as sub-investigators.

The investigator must ensure that patients receive study drug only from personnel who fully understand the procedures for dosing and administering the drug.

Each shipment of study drug for a study will contain an Investigational Drug Shipping Request (IDSR) form to assist the investigator in maintaining current and accurate inventory records.

The IDSR form will identify for each shipment the subject identification code (if applicable), the lot number, and the quantity of vials contained in the shipment. Upon receipt of the investigational drug, the designated recipient will visually inspect the shipment and verify the number and condition of vials received. The designated recipient will complete the lower portion of the IDSR form. A copy of the signed form is to be filed with the inventory/drug accountability records. The original completed form will be mailed back to Astra Zeneca in the envelope provided with the drug shipment.

Only authorized personnel should have access to the drug. For accurate accountability, the following information must be noted when drug supplies are used during the study: the patient identification, the lot number of the drug dispensed for that patient, and the date and quantity of drug dispensed. Study drug accountability records should also document receipt and return or destruction of study drug supplies.

Drug accountability records must be readily available for inspection by representatives of Astra Zeneca and are open to inspection by regulatory authorities at any time.

Compliance of the oral AI will be assessed and recorded by the investigator and/or study personnel at each patient visit. A dosing log will be used.

6.6 Disposition of unused investigational study drug

The site will account for all investigational study drug dispensed and also for appropriate destruction. Certificates of delivery and destruction must be signed.

Return of all drug supplies must be coordinated with Astra Zeneca prior to shipment. When unused drug supplies are returned, the number of vials being returned and the lot numbers should be noted in the site inventory log and the Investigational Drug Return Form provided by Astra Zeneca should be completed.

Upon completion of this study, appropriate site personnel should verify that all unused drug supplies have either been returned or destroyed and that no investigational drug remains in the investigator's possession. For all drug supplies that are not returned, officially signed and dated written documentation of proper disposal or destruction of the drug in accordance with the appropriate

institutional guidelines must be maintained in the drug accountability records. A copy of the drug accountability records must be returned to Astra Zeneca at the end of the study.

6.7 Concomitant Medications and Treatments

The Principal Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit).

The following medications are considered exclusionary:

1. Any investigational anticancer therapy other than the protocol specified therapies
2. Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment, other than any stated comparator or combination regimens. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes) is acceptable. Estrogen-containing hormone replacement therapy is not acceptable.
3. Herbal and natural remedies which may have immune-modulating effects.
4. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).
5. Live attenuated vaccines within 30 days of durvalumab dosing (i.e., 30 days prior to the first dose, during treatment with durvalumab for 30 days post discontinuation of durvalumab. Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

In addition, subjects should not donate blood while participating in this study or for at least 90 days following the last infusion of durvalumab.

6.8 Duration of Therapy

Individual study patients may remain on treatment with an AI in combination with durvalumab until they experience intolerable toxicity, confirmed disease progression, or the investigator determines that the subject is no longer benefiting from treatment (more details are provided in section 4.6.1).

Patients will receive a maximum treatment with 6 cycles of durvalumab.

After the first 6 months, patients will continue receiving the AI at the discretion of the treating physician as per standard of care.

Patients who discontinue active treatment will be followed for recurrence free survival for up to 5 years or until the sponsor ends the study.

7 TOXICITIES AND DOSEAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for adverse event and serious adverse event reporting. A copy of the CTCAE Version 5.0 can be downloaded: (**http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx**).

7.1 Dose Modifications

7.1.1 Aromatase inhibitor

Dose modifications are allowed in case of toxicities thought to be related to the AI. Dose modifications will follow standard of care guidelines and will be at the discretion of the treating physician and Principal Investigator.

Switching to a different AI is permitted. In the safety run-in phase, switching is only allowed outside of the DLT window (details can be found in section 2.5.1).

Dose reductions in AI are not permitted but dose interruptions for up to 14 consecutive days for toxicity reasons is acceptable. Patients may continue to receive durvalumab per the dosing schedule if the toxicity is thought to be caused by the AI.

Patients who can't resume AI treatment after a 14 day hold will discontinue study treatment.

7.1.2 Durvalumab

For adverse events (AEs) that are considered at least partly due to administration of durvalumab, the following dose adjustment guidance may be applied:

- Treat each of the toxicities with maximum supportive care.
- Hold the agent suspected of causing the toxicity when required.
- Dose reductions are not permitted.
- If the symptoms promptly resolve with supportive care, consideration should be given to resuming or continuing the regular dosing schedule of durvalumab along with appropriate continuing supportive care. If medically appropriate, dose delays or interruptions are permitted (see Appendix 1).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

Following the first dose of durvalumab, subsequent administrations can be modified based on toxicities observed (see Appendix 1). In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see Appendix 1).

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing irAEs during the conduct of this study. Potential irAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

Dose modification recommendations and toxicity management guidelines for immune-mediated reactions, for infusion-related reactions, and for non-immune-mediated reactions are detailed in Appendix 1.

In addition, management guidelines for adverse events of special interest (AESIs) are detailed in Section 15.4.4.

7.2 Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating physician including but not limited to the items outlined in the table below:

Rescue/supportive medication/class of drug:	Usage:
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary by the Investigator to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited" as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, growth factor support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc.])	Should be used when necessary for all patients

8 STUDY CALENDAR

8.1 A calendar cycle will last 28 days. Cycles begin the day of a durvalumab infusion. For all visits, there is a ± 3 day window if not explicitly specified otherwise.

Drug administration calendar

Drug	Cycle length (days)	C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1
Anastrozole	**28**	**daily**	**daily**	**daily**	**daily**	**daily**	**daily**
Durvalumab	**28**	**X**	**X**	**X**	**X**	**X**	**X**

Patients who experienced intolerance/toxicities attributable to anastrozole will be allowed to switch to a different AI. For patients in the safety run-in phase, this is allowed only after they have completed the DLT period.

8.2 Schedule of events

Examination	Screening[1]	C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	EOT[136]	Surgery	Follow up[17]
Informed consent	X									
Eligibility review	X									
Medical history	X									
Tumor tissue collection	X[2]		X						X	
Physical examination with ECOG[3]	X	X	X	X	X	X	X	X		X
Vital signs[4]	X	X	X	X	X	X	X	X		X
ECGs[5]	X	X								

Adverse events	X	X	X	X	X	X	X	X		X
Conmeds	X	X	X	X	X	X	X	X		X
Hematology[5][6]	X	X	X	X	X	X	X	X		X
Chemistry[6][7]	X	X	X	X	X	X	X	X		X
Endocrine function tests[7][8]	X	X	X	X	X	X	X	X		
Coagulation[8][9]	X									
Urinalysis[9][10]	X	X	X	X	X	X	X	X		
Serum & plasma collection[10][11]		X	X		X			X		
Tumor assessment[12]	X		X					X		
Assessment of response by exam[13]		X	X					X		
Assessment of response by MRI[14]	X		X					X		
mPEPI[15]									X	

Abbreviations: C, cycle; Conmeds, concomitant medications; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; mPEPI, modified Prepoperative Endocrine Prognostic Index.

[1] Screening laboratory assessments performed within 7 days prior to C1D1 do not need to be repeated.

[2] Core biopsy will be obtained at baseline, after one cycle (1 month +/- 7 days) and at definitive surgery (mandatory). Baseline core biopsy may be omitted at the discretion of the PI.

[3] Full physical examination at screening; targeted physical examination at minimum at other time points. If physical exam, including tumor assessment, is performed within 7 days prior to C1D1 of treatment, no need to repeat physical exam on C1D1.

[4] Blood pressure (BP) and pulse will be measured before, during, and after the infusion at the following time points: beginning of infusion (0 min), halfway through the infusion (30 ± 5 min), end of the infusion (60 ± 5 min), 60 min of observation after the end of C1 infusion (120 ± 5 min). If no issue with C1, observation period can be shortened to 30 minutes after the end of each subsequent cycle. More frequent monitoring can be done as clinically indicated. For infusions taking ≥ 60 min, BP and pulse should be measured following the principles described above. After the first infusion monitoring can be as clinically indicated.

[5] In Screening, 12-lead ECGs (in triplicate 2-5 minutes apart). On C1D1, A 12-lead ECG within 1 hour pre-infusion and 0-3 hours post end of infusion . Other ECGs as clinically indicated. In case of a clinically significant ECG abnormality, including QTcF value > 470 ms, two additional ECGs collected 2-5 minutes apart should be obtained to confirm the findings. In this case, the final QTcF value will be the mean QTcF value calculated from all 3 ECGs.

[6] Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (total neutrophil count including lymphocyte, monocyte, eosinophil and basophil counts), platelet count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration.

[7] Clinical chemistry: sodium, potassium, chloride, carbon dioxide, alkaline phosphatase, AST, ALT, BUN, glucose, creatinine, calcium, total protein, albumin, total bilirubin (direct and indirect bilirubin will be measured if total bilirubin is ≥ 2 x ULN with no evidence of Gilbert's syndrome), lactate dehydrogenase (LDH), magnesium, uric acid, amylase, lipase, GGT. Clinical chemistries due at screening, prior to each infusion, and at EOT. Results for liver panel (AST, ALT, alkaline phosphatase, bilirubin) must be available and reviewed before starting an infusion. Amylase and lipase due at screening, the start of each new cycle, and EOT. GGT due at screening, C1D1, and as clinically indicated.

[8] Endocrine function tests: Thyroid-stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4), cortisol, adrenocorticotropic hormone (ACTH). TSH due at screening and the start of each new cycle. Free T3 and free T4 due if TSH is abnormal or if there is suspicion of an endocrine-related AE. Cortisol and ACTH due as clinically indicated.

[9] Coagulation parameters: prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)

[10] Urinalysis: color and appearance, pH, specific gravity, bilirubin, blood protein, glucose, ketones. Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.

[11] To be collected prior to C1D1, prior to C2D1, prior to C4D1, and at end of C6. For [11], prior = either the day before or prior to therapy.

[12] Mammogram, ultrasound of the ipsilateral breast within 60 days of the start of treatment. MRI of ipsilateral breast at baseline, end of cycle 1 (+/- 7 days), and at end of treatment prior to definitive surgery. Mammogram of the contralateral breast within 12 months of the start of treatment. Staging scans (CT chest, abdomen +/- pelvis and bone scan or PET/CT) should be considered, per institutional standard practice. Otherwise, staging scans should be obtained if clinically indicated.

[13] If tumor assessment by exam is performed at screening within 7 days prior to C1D1 of treatment, no need to repeat tumor assessment by exam on C1D1.

[14] MRI of ipsilateral breast at end of cycle 1 may be omitted at the discretion of the PI.

[15] mPEPI score will include tumor size and nodal status based on final pathology report for the definitive surgery as well as Ki67 value of the tumor from the definitive surgery.

[16] EOT is defined as the end of cycle 6 (28 +/- 7 days from C6D1) . For subjects who discontinue treatment early, EOT is considered as visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 7 days of the EOT visit. Repeat imaging disease assessment is not required if performed within 28 days prior to the end of treatment visit.

[17] First follow up visit will occur 90 to 97 days from last study treatment (durvalumab). The time to first follow up visit may be longer than 97 days, but in no case should it be <90 days. If first study visit is competed before 90 days after last durvalumab, the patient will be contacted 90 to 97 days following the last treatment to assess for adverse events. After all study therapy has been completed, patients will be followed for recurrence and survival for up to 5 years after registration (every 6 months +/- 1 month per either medical records or phone calls).

9 STUDY PROCEDURES

9.1 Screening phase

The following screening procedures will be performed up to 28 days before Day 1, unless otherwise specified. Procedures that are performed prior to the signing of the informed consent form (ICF) and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window. There is no time limitation on the standard of care biopsy to establish the diagnosis and to determine the receptor status.

- Informed consent.
- Review of eligibility criteria.
- Medical history and demographics.
- Review of prior/concomitant medications.
- Complete physical exam including assessment of palpable tumor and ECOG Performance Status.
- Vital signs, weight and height 12-lead ECGs (in triplicate 2-5 minutes apart).
- Staging scans (CT chest, abdomen +/- pelvis or PET/CT) are not mandatory but should be considered as per institutional standard of practice. Otherwise, staging scans should be obtained if clinically indicated.
- Archival tumor tissue (detailed requirements in section 9.4.6) and fresh tumor biopsy. Fresh tumor biopsy at baseline may be omitted at the discretion of the PI.
- Clinical laboratory tests (see section 9.4.5 for details):
    - Hematology
    - Clinical chemistry
    - Thyroid function tests (TSH, free T3, free T4)
    - Coagulation
    - Creatinine Clearance
    - Urinalysis

9.2 Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Events (sections 8.1 and 8.2). Screening procedures performed within 7 days of C1D1 do not need to be repeated on C1D1.

On the first day of each cycle:

- Physical examination, including assessment of palpable tumor, ECOG performance status, vital signs (including infusion monitoring as described in section 9.4.4), and weight.
- Assessment of adverse events and collection of concomitant medications. A 12-lead ECG within 1 hour pre-infusion and 0-3 hours post end of infusion on C1D1

only; and single ECG as clinically indicated. In case of a clinically significant ECG abnormality, including QTcF value ≥ 470 ms, two additional ECGs collected 2-5 minutes apart should be obtained to confirm the findings. In this case, the final QTcF value will be the mean QTcF value calculated from all 3 ECGs.

- Hematology.
- Clinical chemistry.
    - ***Results from the liver panel must be received prior to dosing.***
    - GGT is only due on C1D1 and as clinically indicated.
- Endocrine functions tests: TSH, free T3 and free T4 (only if TSH is abnormal or if there is clinical suspicion of an adverse event related to the endocrine system), ACTH and cortisol (if indicated).
- Urinalysis.
- Coagulation parameters as clinically indicated.
- Correlative blood samples per Schedule of Events.
- Administration of study treatments with an AI and durvalumab (on C1D1, patients are to take AI prior to infusion of durvalumab).
- Tumor biopsy at the end of cycle 1 prior to C2D1 (within 7 days). May be omitted at the discretion of the PI.

9.3 End of Treatment Visit (28 +/- 7 days after last dose of durvalumab)

End of treatment is defined as the end of cycle 6 (28 +/- 7 days from C6D1). For subjects who discontinue durvalumab prior to 6 months, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 7 days of the end of treatment visit. Repeat imaging disease assessment is not required if performed within 28 days prior to the end of treatment visit.

- Physical examination, including assessment of palpable tumor, ECOG performance status, vital signs (including infusion monitoring as described in section 9.4.4), and weight.
- Assessment of adverse events and collection of concomitant medications.
- Hematology.
- Clinical chemistry.
- Endocrine functions tests.
- Correlative blood samples per Schedule of Events.
- Administration of study treatments with an AI and durvalumab (if applicable)
- Breast imaging for disease assessment for all patients. Ipsilateral breast mammogram, ultrasound and/or breast MRI are acceptable, provided that the same method is used throughput for an individual patient.
- If clinically indicated: urinalysis, coagulation parameters, 12-lead ECG.

All subjects will be followed for recurrence free survival until the end of the study, or until the sponsor ends the study.

9.4 Description of Study Procedures

9.4.1 Medical history

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

9.4.2 Physical examination

Physical examinations will be performed according to the assessment schedule. 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.

9.4.3 Vital signs

Vital signs (blood pressure, pulse, temperature, and respiration rate) and body weight will be evaluated according to the assessment schedules.

Supine BP will be measured using a semi-automatic BP recording device with an appropriate cuff size, after the patient has rested for at least 5 minutes. BP and pulse will be collected from patients receiving durvalumab treatment before, during, and after each infusion at the following times (based on a 60-minute infusion):

1. Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to the beginning of the infusion which is t = 0 minutes).
2. Approximately 30 minutes into the infusion (halfway through infusion).
3. At the end of the infusion (approximately 60 minutes ± 5 minutes).
4. A 1-hour observation period is required after the first infusion of durvalumab.

If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab infusion).

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. The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

9.4.4 Clinical laboratory tests

The following clinical laboratory tests will be performed per the Schedule of Assessments:

- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (total neutrophil count including lymphocyte, monocyte, eosinophil and basophil counts), platelet count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration.
- Clinical chemistry: sodium, potassium, chloride, carbon dioxide, alkaline phosphatase, AST, ALT, BUN, glucose, creatinine, calcium, total protein, albumin, total bilirubin (direct and indirect bilirubin will be measured if total bilirubin is $\geq$ 2 x ULN with no evidence of Gilbert's syndrome), lactate dehydrogenase (LDH), magnesium, uric acid, amylase, lipase, GGT.
- Coagulation parameters: prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR).
- Endocrine function tests: TSH, free T3, free T4, cortisol, adrenocorticotropic hormone (ACTH).
- Urinalysis: color and appearance, pH, specific gravity, bilirubin, blood protein, glucose, ketones. Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.

9.4.5 Correlative samples

Correlative blood samples

Blood samples for correlative studies will be collected for the following tests as well as stored for future research:

- Cytokine level measurement (before C1D1, C2D1, C4D1 and end of C6 or EOT).

Additional details about correlative blood samples are provided in section 14.4.

Archival tumor samples and fresh tumor biopsies

Tumor tissue samples will be collected before the first study treatment, at the end of cycle 1 (within 7 days), and from the definitive surgical specimens. Collection of fresh tissue samples may be omitted at the discretion of the PI.

Archival tissue is acceptable for enrollment after confirmation that stored tissue blocks are of adequate quality and can yield a minimum of 10 sections each 4 to 5 microns thick. A fresh biopsy is mandatory if the amount of archival tissue is insufficient.

Fresh tumor tissue collection via ultrasound-guided core biopsy is mandatory once a patient has completed one cycle of treatment (collection to be within 7 days of the end of a cycle). However, this may be omitted at the discretion of the PI.

Tumor tissue samples will be analyzed for changes in PD-L1 expression, changes in subtypes of immune infiltrates, cytokine patterns, and levels of Ki-67 expression.

Further details about sample collection, storage, and testing are provided in the laboratory manual and in sections 14.1 and 14.2.

10 CRITERIA FOR EVALUATION AND ENDPOINT

10.1 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

The type, incidence, severity, timing, seriousness, and relatedness of adverse events and laboratory abnormalities will be assessed and recorded.

10.2 Efficacy

Tumor response will be assessed by clinical breast examination (CBE), which includes examination of the breast, axilla, and supraclavicular fossa. Tumor assessment by imaging is required prior to surgery.

Evaluation by Clinical Exam or Imaging

The following definition of response will be used for objective clinical response rate:

Clinical complete response (CR): Palpable lesion(s) identified at baseline are no longer palpable and there are no new lesion(s) or other signs of disease progression.

Clinical partial response (PR): A reduction in the product of the two largest perpendicular diameters of the primary tumor by 50% or more.

Clinical progression of disease (PD): An increase in the product of the two largest perpendicular diameters of the primary tumor by 25% or more or the presence of a new lesion.

Clinical stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Evaluation by pathologic Assessment:

All patients will be followed through their post-treatment standard of care surgery to evaluate pathologic response per local pathologist's assessment. Pathologic complete response is defined as no histologic evidence of invasive tumor cells in the surgical breast specimen, axillary nodes, or non-axillary sentinel nodes (SNs) identified after neoadjuvant therapy.

10.3 Stopping Rules

Safety run-in phase: Refer to section 4.2 for definition and evaluation of Dose Limiting Toxicities.

Extension phase: Based on a Simon's two stage Optimum design (see statistical details in section 11.3), an initial analysis will be done on the first 14 evaluable patients (this includes the 6 patients in the safety run-in phase). Recruitment will be terminated if an mPEPI 0 is achieved in 0 or 1 patients. If 2 or more patients achieve an mPEPI 0 the

study will proceed to enroll until a total of 42 evaluable patients have been accrued (for an estimated total of 46 patients assuming a 10% nonevaluability).

11 STATISTICAL CONSIDERATIONS

11.1 Description of analysis sets

11.1.1 Safety analysis set

Safety run-in phase: The safety analysis set will include all subjects who received at least 1 dose of AI or durvalumab, and had adverse events recorded at all visits up to and including C2D1 (prior to cycle 2 infusion) or had experienced a DLT at one or more visits up to and including C2D1 (prior to cycle 2 infusion).

Extension phase: The safety analysis set will include all subjects who received at least one dose of AI or durvalumab.

11.1.2 Efficacy analysis set

The efficacy analysis set will include all subjects in both safety run-in phase and extension phase of the study who received at least 1 planned dose of AI and durvalumab.

11.2 Methods of statistical analyses

11.2.1 Safety Analyses

Safety data will be summarized for all patients receiving at least 1 dose of study treatment.

All patients who receive any study treatment will be included in the final summaries and listings of safety data. Detailed information collected for each AE will include a description of the event, duration, severity, relatedness to study drugs, action taken, and clinical outcome. Severity of the AEs will be graded according to the CTCAE version 5.0.

The DLT analysis will include the 6 DLT evaluable subjects enrolled in the safety run-in phase who must have had the opportunity to be on treatment for 1 cycle (4 weeks) from the initial dosing of durvalumab and received at least 1 dose of AI and one dose of durvalumab.

11.2.2 Efficacy Analyses

Primary Endpoint: A Simon's two-stage Optimum design will be used in which the drug will be determined to be efficacious if 7 or more patients achieve an mPEPI of 0. The study will stop after the first 14 patients are enrolled if 1 or fewer patients achieve an mPEPI of 0.

Secondary Endpoints: The best response, including complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), for each patient will also be summarized with 95% confidence intervals. Descriptive statistics will be used to

summarize all patient characteristics, treatment administration and compliance. Kaplan-Meier curves will be used to estimate the median recurrence free survival time.

11.3 Determination of sample size

Sample Size Justification/Statistical Analysis:

A Simon two-stage Optimum design will be used in phase 2 for the calculation of sample size. Achieving mPEPI 0 in less than 10% of the patients is non desirable (response probability of poor drug P0 = 0.10) and we aim to achieve mPEPI 0 in at least 25% of the patients (response probability of good drug P1 = 0.25). The type I error rate and power were set to 0.10 and 85%, respectively. The first stage sample size is 14 evaluable patients. If 2 or more patients achieve mPEPI 0 among the first 14 evaluable patients the study will continue to enroll until reaching the maximum sample size of 42 (for an estimated total of 46 patients assuming a 10% nonevaluability). The treatment would be considered worthwhile for further study if 7 or more patients out of the 42 achieve mPEPI 0. The probability of early termination is 0.585 and the expected sample is 25.63. Note, PEPI score 0 was obtained in approximately 16% of patients with AI alone (5)[3]. However, in this study, clinical T2 N0 stage accounted for approximately three quarters of the study population. Knowing our patient population and referral patterns for neoadjuvant therapy for ER+ disease, we projected that the vast majority of patients referred to this study would be clinically node positive (at least N1) and/or T3, either or both of which could and would greatly reduce the rate of PEPI score 0. That was the reason for our setting the non-desirable rate at a lower number, 10% instead of 16%.

12 REGISTRATION GUIDELINES

All subjects must personally sign and date the consent form before commencement of study-specific procedures (i.e., non-standard of care procedures).

All subjects who enter into the screening period for the study (defined as the point when the subject signs the informed consent) must be registered as screened subjects and will receive a unique subject identification number before any study-specific procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

Subjects that are determined to be eligible for study entry will be enrolled in the study. Subjects that are determined not eligible must be designated as screen failures, and the reason for the screen-failure provided. Subjects who do not meet all eligibility criteria may be rescreened once at the discretion of the investigator. If a subject is being rescreened, he or she may need to reconsent to the study to ensure that the Institutional Review Board (IRB)-approved informed consent form has been signed within 28 days of enrollment. Subjects who are determined ineligible after rescreening must be designated as screen-failures, and the reason for the screen failure must be provided.

Subjects who fail to meet the inclusion criteria or who meet the exclusion criteria should not, under any circumstances, be enrolled. There can be no exceptions to this rule. Where

subjects who do not meet the selection criteria are incorrectly started on treatment, or where subjects subsequently fail to meet the study criteria post initiation, a discussion will occur between the Principal Investigator and the Protocol Monitoring Committee regarding whether to continue or discontinue the subject from treatment. The PI and the PMC are to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the subject should have their study therapy stopped.

Treatment should start within five working days after registration. The registration date will be the enrollment date.

To register eligible patients on study, patients must sign an informed consent prior to screening and registration indicating awareness of the investigation nature of the study. Eligibility will be centrally reviewed by the Moffitt Monitoring Core following completion and investigator certification of a Moffitt approved eligibility checklist. The checklist will be emailed to monitoring.core@moffitt.org during regular business hours. After monitoring core QA review is complete, patients will be registered into Oncore on study and initiate study treatment.

13 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of electronic forms for each patient that provides a record of the data generated according to the protocol. CRF's should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. **Data capture should be restricted to endpoints and relevant patient information required for planned manuscripts.** These forms will be completed on an on-going basis during the study. The medical records will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Protocol Monitoring Committee. The Investigator will allow the Protocol Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

14 SPECIAL INSTRUCTIONS

14.1 Tumor tissue for PD-L1 testing

Preferred baseline sample for PD-L1 testing are less than or equal to 3 months old. In cases where an archived sample less than 3 months old is not available, patients will be asked to undergo a new biopsy if considered clinically appropriate by their treating physician.

Fresh samples should be collected via a core needle of 18 gauge or larger or be collected by an incisional or excisional tumor biopsy. Where institutional practice uses a smaller

gauge needle, samples should be evaluated for tumor cell quantity (i.e. >100 tumor cells) to allow for adequate PD-L1 immunohistochemistry analyses.

Samples submitted for PD-L1 testing should be formalin fixed and embedded in paraffin. Samples from fine needle aspirates (FNA) are not appropriate for PD-L1 analysis. A minimum of 5 slides 4 to 5 microns in thickness is required for testing.

To ensure comparability of data across all studies of durvalumab and/or tremelimumab and to gain real world experience on the performance of this assay, it is encouraged that all studies that include PD-L1 testing utilize the Ventana SP263 assay.

14.2 Tumor tissue for other testing

Tumor tissue samples embedded in paraffin will also be analyzed by hematoxylin-eosin and immunohistochemical staining for several biomarkers, including biomarkers of immune cell response (i.e., CD3, CD4, CD8, CD56), immune cell activation (i.e., CD45RO, HLA-DR, CD137), proliferation (Ki67) (Ki67 will be obtained on both tumor cells and T cells), Treg phenotype (i.e., CD4/CD25/FOXP3).

Frozen tumor tissue samples will be stored for future studies (including TCR sequencing and the generation of tumor-infiltrating lymphocytes and the characterization of their phenotype and function as well as generation of tumor clones and the characterization of their phenotypes and mutational status).

A minimum of 5 slides 4 to 5 microns in thickness is required for the above testing.

14.3 Other correlative studies

Serum and plasma will be collected at baseline, the end of cycle 1, of cycle 3, and of cycle 6 or EOT . Serum will be tested for cytokine levels using ELISA. The rest of the serum and plasma will be stored for future studies.

Estimates for total blood volume collections are as follows:

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety:	Clinical chemistry	7	6-12	42-84
	Hematology	7	6-12	42-84
Biomarker (serum/plasma)		60	4	240
Total				324-408

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Informed consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB approved version.

15.2 Institutional Review

Study will be approved by a central Institutional Review Board.

15.3 Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

15.3.1 This study will utilize the CTCAE Version 5.0 for AE and SAE reporting. An electronic copy of the CTCAE Version 5.0 can be downloaded from http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspxAdverse Events (AE)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy. Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE.

The collection of adverse events will begin after first study drug administration and end 90 days post last dose of study treatment or initiation of a new anticancer therapy, whichever comes first.

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. After 90 days, only subjects with ongoing investigational product-related SAEs will continue to be followed for safety.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- Its severity grade based on CTCAE v. 5.0 (grade 1 to 5).

- Its relationship to each of the study drugs (definite, probable, possible, unlikely, and not related).
- Its duration (start and end dates or if continuing at final exam).
- Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization).
- Whether it constitutes an SAE.

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose interruption and modification section of this protocol (see section 7.1 for guidance). Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the study drugs drug are described in the drug information section (section 3.1), the most recent investigator brochures (for durvalumab), and the FDA-approved product labels (for the three AIs). This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

All adverse events will be recorded in the subject specific AE log.

15.3.2 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded. **Moffitt Cancer Center and all participating sites will report SAEs by completing an SAE report in ONCORE, the electronic data capture system.**

A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening.
- Results in persistent or significant disability/incapacity.
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.
- Causes congenital anomaly or birth defect.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, and pain control).
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug.

- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
- Social reasons and respite care in the absence of any deterioration in the patient's general condition.

Toxicities which fall within the definitions listed above must be reported as an SAE regardless of whether they are felt to be treatment related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above, must simply be documented as AEs in the patient research chart

The collection of serious adverse events will begin after signature of the ICF and end 90 days post last dose of study treatment or initiation of a new anticancer therapy, whichever comes first. If a subject discontinues 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.

In addition to capturing all information required for an AE, the following information will be collected for SAE as applicable:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Which criterion makes the AE serious
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Additional Study Drug

15.3.3 Death

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

- Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported as an SAE. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as a SAE.

Any death which occurs more than 90 days after protocol treatment has ended but which is felt to be treatment related, must be reported.

15.3.4 Adverse events of special interest

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

AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the Investigator has any questions in regards to an adverse event (AE) being an irAE, the Investigator should promptly contact the Principal Investigator.

AESIs 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)
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological and rheumatological events.

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

- Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochures. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Appendix 1). These guidelines have been prepared by AstraZeneca to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

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

For durvalumab, AESIs will comprise the following:

Pneumonitis

AEs of pneumonitis are of interest for AstraZeneca, as pneumonitis has been observed with use of anti-PD-1 mAbs (but not with anti-PD-L1 mAbs). Initial work-up should include a high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended. Guidelines for the management of patients with immune-related AEs (irAEs) including pneumonitis are provided in Appendix 1.

Infusion reactions

AEs of infusion reactions (also termed infusion-related reactions) are of special interest to AstraZeneca and are defined, for the purpose of this protocol, as all AEs occurring from the start of IP infusion up to 48 hours after the infusion start time.

Hypersensitivity reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti PD-L1 and anti-PD-1 therapy (44). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the mAbs and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness. Guidelines for the management of patients with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are provided in Appendix 1.

Hepatic function abnormalities (hepatotoxicity)

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated

promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the IP. Guidelines for management of patients with hepatic function abnormality are provided in Appendix 1.

Gastrointestinal disorders

Diarrhea/colitis is the most commonly observed treatment emergent SAE when tremelimumab is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Guidelines on management of diarrhea and colitis are provided in Appendix 1.

Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in Appendix 1.

Pancreatic disorders

Immune-mediated pancreatitis includes autoimmune pancreatitis, and lipase and amylase elevation. Guidelines for the management of patients with immune-mediated pancreatic disorders are provided in Appendix 1.

Neurotoxicity

Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Appendix 1.

Nephritis

Consult with Nephrologist. Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc)

Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, etc.).

Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2) in order to prevent potential progression to higher grade event. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Appendix 1.

15.3.5 Immune-related adverse events

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is a possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab, BMS-936558 (anti-PD-1 mAb), and BMS-936559 (anti-PD-L1 mAb) and may include immune-

mediated enterocolitis, dermatitis, hepatitis (hepatotoxicity), pneumonitis, and endocrinopathies). **Error! Bookmark not defined.**,[1] These AEs are inflammatory in nature and can affect any organ. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, dermatitis, pneumonitis, hepatitis, and endocrinopathy. In addition to the dose modification guidelines provided in Appendix 1, it is recommended that irAEs are managed according to the general treatment guidelines outlined for ipilimumab. These guidelines recommend the following:

- Patients should be evaluated to identify any alternative etiology.
- In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune related.
- Symptomatic and topical therapy should be considered for low-grade events.
- Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
- More potent immunosuppressives should be considered for events not responding to systemic steroids (e.g., infliximab or mycophenolate).
- If the Investigator has any questions in regards to an AE being an irAE, the Investigator should immediately contact the PI.

15.3.6 Potential drug-induced liver injury

The combination of increased transaminases plus increased total bilirubin may be indicative of drug-induced liver injury (DILI), and should be considered as clinically important events. Patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT, AST, and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin >2.0 x ULN.
- For patients with elevated AST, ALT, or total bilirubin value at baseline: AST or ALT > 2 x baseline and > 3.0 x ULN OR AST or ALT > 8.0 x ULN, whichever is lower, combined with total bilirubin > 2 x baseline and > 2.0 x ULN.

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as an alkaline phosphatase elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of alkphos liver fraction in patients with bone metastasis.

Note: The R value is calculated by dividing the ALT by the alkphos, using multiples of the ULN for both values [R value = (ALT/ULN)/(alkphos/ULN)]. It denotes the relative pattern of ALT and/or alkphos elevation is due to cholesteric or hepatocellular liver injury or mixed type injury.

An R value > 5.0 is used to define hepatocellular injury, R < 2.0 as cholestatic injury, and R between 2.0 to 5.0 as mixed hepatocellular-cholestatic injury.

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant", thus met the definition of SAE, and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

15.4 SAE Reporting Requirements

SAEs must be reported concurrently to the IRB according to IRB policy and AstraZeneca within 24 hours of learning of the event.

All SAEs will be reported to the Clinical Trial Office of Moffitt Cancer Center in 24 hours via ONCORE. .

External sites should abide by local IRB requirements for submission of SAEs.

AstraZeneca Notifications:

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of durvalumab or until the initiation of alternative anticancer therapy. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

The Investigator (or other designated site personnel) must notify the appropriate AstraZeneca representative of an SAE **no later than 24 hours after becoming aware of the event.**

The designated AstraZeneca representative will work with the Investigator to ensure that all necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events and **within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE **no later than 24 hours** of becoming aware of it.

A MedWatch 3500A form must be completed along with a cover page indicating the following:

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address

- The trial name/title and AstraZeneca ISS reference number (ESR-17-13182)

The investigator must also ensure that either the SAE report or the cover page detail the causality of the event in relation to all study medications and whether the event is related to disease progression, as determined by the principal investigator.

SAE reports and accompanying cover pages will be sent via email to AstraZeneca's designated mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com
If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.

Serious adverse events that do not require expedited reporting to the FDA still need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

15.5 Other events requiring reporting

15.5.1 Overdose

An overdose is defined as a subject 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 subject with durvalumab, with or without associated AEs/SAEs, is required to be reported **within 24 hours of knowledge of the event** to the Principal Investigator, the PMC (via the RCO), and AstraZeneca/MedImmune Patient Safety or designee using the designated safety e-mailbox (see Section 15.5 for contact information).

If the overdose results in an AE, the AE must also be recorded as such. 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. The investigator will use clinical judgment to treat any overdose.

15.5.2 Hepatic function abnormality

Hepatic function abnormality (as defined in section 15.4.6) in a study subject, 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 Principal Investigator, the PMC (via the RCO), and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox (see Section 15.5 for contact information), unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

- 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 subject will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject 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 Principal Investigator, the PMC, and AstraZeneca/MedImmune.

15.6 Protocol Amendments

Any amendments or administrative changes in the research protocol during the period for which the IRB approval has already been given will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

15.7 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the **prompt reporting** of protocol deviations which meet any of the following criteria:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant.
- Harmful (caused harm to participants or others, or place them at increased risk. harm - including physical, psychological, economic, or social harm).
- Possible serious or continued noncompliance.

15.8 FDA Annual Reporting

An annual progress report will be submitted to the FDA within 60 days of the anniversary of the date that the IND went into effect. [21 Code of Federal Regulations (CFR) 312.33]. Content of this report is listed in Appendix III.

15.9 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

16 DATA MANAGEMENT

16.1 Data Collection

The Clinical Research Coordinators, Data Specialists, and Investigators of each site will be responsible for the recording of the site's data into the electronic data capture system, ONCORE.

16.2 Protocol Monitoring Committee

The Protocol Monitoring Committee (PMC) will be composed of medical and statistical independent reviewers and will meet to review the efficacy and safety data and determine a risk/benefit analysis in this subject population. The purpose of the PMC is to advise on serious safety considerations, lack of efficacy and any other considerations within the charge to the Committee. The PMC may request additional meetings or safety reports as deemed necessary upon discussion with the principal investigator. The PMC may stop the study following review of results from each interim analysis. The PMC meets monthly and reviews accrual, patterns and frequencies of all adverse events, protocol violations and when applicable, internal audit results.

16.3 Study Monitoring and Auditing

16.3.1 Investigator Responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

Investigators, or a designated member, must enter study data onto CRFs or other data collection system. The Investigator will permit study-related monitoring visits and audits by AstraZeneca or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available to the AstraZeneca representative so that the accuracy and completeness may be checked.

16.3.2 Site Responsibilities

A conference call/study meeting will be held monthly to review patient enrollment and accrual, safety and toxicity data, and treatment results, as available.

16.3.3 Monitoring

Monitoring will be performed regularly by the MCC Clinical Monitoring Core for accuracy, completeness, and source verification of data entry, validation of appropriate informed consent

process, reporting of SAEs, and adherence to the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements

Data will be captured in Oncore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. The monitoring will include source data verification, utilizing research subjects' medical records.

The Sponsor maintains a robust pharmacovigilance system comprising a governance framework and standard operating procedures supporting a systematic process for review, evaluation, and management of accumulating safety data from clinical trials and other sources to identify a potential new safety signal and ensure that an investigational product's risks are adequately assessed and communicated to investigators, IRBs/IECs, and regulatory bodies during clinical development.

For this study, safety monitoring activities will include but are not limited to review and evaluation of single serious adverse event (SAE) occurrences in real-time as reported through the SAE reporting process outlined in this section of the protocol, and review and evaluation, in real-time, of one or more occurrences of an uncommon SAE that is not commonly associated with product exposure.

Findings and/or safety data obtained during this study will provide information for the overall review of safety that is conducted by the Sponsor on a routine basis. The Sponsor will report expeditiously any findings from clinical trials (ongoing or completed), epidemiological studies, pooled analysis of multiple studies, and findings from animal or *in vitro* testing that suggest a significant risk in humans exposed to the study product.

Safety data collection for this study begins at the time of the subject's receiving the first dose of study medication. The investigator is responsible for the detection and documentation of events that meet the definition of an unanticipated problem, AE or SAE.

17 BIBLIOGRAPHY

1. Siegel, RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.
2. Keen JC, Davidson NE. The biology of breast carcinoma. Cancer 2003; 97: 825–33.
3. Colleoni M, Sun Z, Price KN, Karlsson P, Forbes JF, Thürlimann B, et al. Annual Hazard Rates of Recurrence for Breast Cancer During 24 Years of Follow-Up: Results From the International Breast Cancer Study Group Trials I to V. J Clin Oncol. 2016 Mar 20; 34(9): 927–935.
4. Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. N Engl J Med 2017; 377:1836-1846
5. Ellis MJ, Suman VJ, Hoog J, Lin L, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype--ACOSOG Z1031. J Clin Oncol. 2011. 29(17):2342-9.
6. Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. Contemp Clin Trials. 2008 Jul;29(4):456-65.
7. https://www.allianceforclinicaltrialsinoncology.org/main/cmsfile?cmsPath=/Public/ Annual%20Meetin g/files/Alliance%20A011106%20.pdf
8. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004;22:329-60.
9. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol. 2008;26:677-704.
10. Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol. 2007 Jul;19(7):813-24. Epub 2007 Jul 2.
11. Sharpe AH, Wherry EJ, Ahmed R, Freeman GJ. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nat Immunol. 2007 Mar;8(3):239-45.
12. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.
13. Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012 Jun;366 (26):2455-65.

14. Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res. 2005;65(3):1089-96.

15. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA. 2002 Sep 17;99:12293-7.

16. Okudaira K, Hokari R, Tsuzuki Y, Okada Y, Komoto S, Watanabe C, et al. Blockade of B7-H1 or B7-DC induces an anti-tumor effect in a mouse pancreatic cancer model. Int J Oncol. 2009 Sep;35(4):741-9.

17. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366:2443-54.

18. Zhang C, Wu S, Xue X, Li M, Qin X, Li W, et al. Anti-tumor immunotherapy by blockade of the PD-1/PD-L1 pathway with recombinant human PD-1-IgV. Cytotherapy. 2008;10(7):711-9.

19. Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature. 2014 Nov 27;515(7528):558-62.

20. Rizvi N, Brahmer J, Ou S-H, Segal NH, Khleif SN, Hwu WJ. Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand-1 (PD-L1) antibody, in patients with nonsmall cell lung cancer (NSCLC). J Clin Oncol 2015;33:Abstract 8032.

21. Segal NH, Ou S-HI, Balmanoukian AS, Fury MG, Massarelli E, Brahmer JR, et al. Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. J Clin Oncol 2015;33:Abstract 3011.

22. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Blankin AV, et al. Signatures of mutational processes in human cancer. Nature. 2013 Aug 22;500:415-21.

23. Nanda R, Chow LQM, Dees EC, Berger R, Gupta S, Geva R, et al. Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study. Journal of Clinical Oncology 2016. 34 (20): 2460-2467.

24. Tolaney S, Savulsky C, Aktan G, Xing D, Almonte A, Karantza V, et al. Phase 1b/2 study to evaluated eribulin mesylate in combination with pembrolizumab in patients with metastatic triple-negative breast cancer. Presented at the 2016 San Antonio Breast Cancer Symposium;December 6-10, 2016, San Antonio, TX; abstr P5-15-02.

25. Adams S, Diamond JR, Hamilton EP, Pohlmann PR, Tolaney SM, Molinero L. Phase Ib trial of atezolizumab in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer (mTNBC).

26. http://www.ascopost.com/News/59027

27. Rugo HS, Delord JP, Im SA, Ott PA, Piha-Paul SA, Bedard PL et al. Safety and Antitumor Activity of Pembrolizumab in Patients with Estrogen Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer. Clin Cancer Res; 24(12); 2804-11

28. Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res 2015; 3(9):1052-62.

29. Behjati S, Frank MH. The effects of tamoxifen on immunity. Curr Med Chem. 2009;16:3076–80.

30. Wang JX, Zhang QY, Jin S, Feng MY, Kang XM, Zhao S, et al. Immoderate inhibition of estrogen by anastrozole enhances the severity of experimental polyarthritis. Exp Gerontol. 2009; 44:398–405.

31. Mello-Grand M, Singh V, Ghimenti C, et al. Gene expression profiling and prediction of response to hormonal neoadjuvant treatment with anastrozole in surgically resectable breast cancer. Breast Cancer Res Treat. 2010; 121(2):399-411.

32. Mehta NR, Wurz GT, Burich RA, Greenberg BE, Griffey S, Gutierrez A, et al. L-BLP25 vaccine plus letrozole induces a TH1 immune response and has additive antitumor activity in MUC1-expressing mammary tumors in mice. Clin Cancer Res. 2012; 18:2861–71.

33. Generali D, Bates G, Berruti A, et al. Immunomodulation of FOXP3+ Regulatory T Cells by the Aromatase Inhibitor Letrozole in Breast Cancer Patients. Clin Cancer Res (2009) 15; 1046-1051.

34. Zhang Q, Tang D, Zhao H. Immunological therapies can relieve aromatase inhibitor-related joint symptoms in breast cancer survivors. Am J Clin Oncol. 2010; 33(6):557-60.

35. Chen J, Feng Y, Lu L, et al. Interferon-γ-induced PD-L1 surface expression on human oral squamous carcinoma via PKD2 signal pathway. Immunobiology. 2012; 217(4):385-93.

36. Abiko K, Matsumura N, Hamanishi J, et al. IFN-γ from lymphocytes induces PD-L1 expression and promotes progression of ovarian cancer. Br J Cancer. 2015; 112(9):1501-9.

37. Muenst S, Schaerli AR, Gao F, et al. Expression of programmed death ligand 1 (PD-L1) is associated with poor prognosis in human breast cancer. Breast Cancer Res Treat. 2014 Jul;146(1):15-24

38. Yardley D, Green N, Papish S, et al. Rheumatologic Evaluation of Adjuvant Letrozole in Post-Menopausal Breast Cancer Patients Discontinuing Anastrozole Due to Grade 2-3 Arthralgia – Myalgia. Cancer Res 2009, 69:805

39. Fairman D, Narwal R, Liang M, Robbins PB, Schneider A, Chavez C, et al. Pharmacokinetics of MEDI4736, a fully human anti-PDL1 monoclonal antibody, in

Patients with advanced solid tumors. Journal of Clinical Oncology 32, no. 15_suppl (May 20 2014), 2602-2602.

40. Ng CM, Lum BL, Gimenez V, et al. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res. 2006;23(6):1275–84.
41. Wang DD, Zhang S, Zhao H, et al. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009;49(9):1012–24.
42. Zhang S, Shi R, Li C, et al. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol. 2012;52(1):18–28.
43. Narwal R, Roskos LK, Robbie GJ (2013) Population Pharmacokinetics of Sifalimumab, an Investigational Anti-Interferonalpha Monoclonal Antibody, in Systemic Lupus Erythematosus. Clin Pharmacokinet 52:1017–1027
44. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012 Jun 28;366(26):2455-65.

18 APPENDIX

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions [Durvalumab (MEDI4736)] 1 November 2017 Version

General Considerations

Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v5.0. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤10 mg/day or equivalent. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: • It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. • Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. • Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. • For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. • Some events with high likelihood for morbidity and/or mortality – e.g., myo-carditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. • If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). • More potent immunosuppressives such as TNF inhibitors (e.g., infliximab) (also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions [Durvalumab (MEDI4736)] 1 November 2017 Version

General Considerations

Dose Modifications	Toxicity Management
Grade 4 Permanently discontinue study drug/study regimen. Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. • With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. • Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

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

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for

			general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[a] – Consider pulmonary and infectious disease consult. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Diarrhea/Colitis	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium

		difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and

			anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 (AST or ALT >ULN and ≤3.0×ULN and/or TB > ULN and ≤1.5×ULN)	• No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – Continue LFT monitoring per protocol.

Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN and/or TB >1.5×ULN and ≤3.0×ULN)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Grade 3 or 4 (Grade 3: AST or ALT >5.0×ULN and ≤20.0×ULN and/or TB >3.0×ULN and ≤10.0×ULN) (Grade 4: AST or ALT >20×ULN and/or TB >10×ULN)	**For Grade 3:** For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

		For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	**General Guidance**	**For Any Grade:** − Consult with nephrologist. − Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). − Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum creatinine > 1 to 1.5 × baseline; >	No dose modifications.	**For Grade 1:** − Monitor serum creatinine weekly and any accompanying symptoms.

ULN to 1.5 × ULN)		• If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV

	creatinine >6.0 × ULN)		methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 5.0 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.

	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation.

		– If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections

		investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	[Category 2B recommendation]).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy,	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v5.0 for defining the CTC	**General Guidance**	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness).

excluding Myasthenia Gravis and Guillain-Barre)	grade/severity)		− Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). − Perform symptomatic treatment with neurological consult as appropriate. −
	Grade 1	No dose modifications.	**For Grade 1:** − See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** − Consider, as necessary, discussing with the study physician. − Obtain neurology consult. − Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). − Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Consider, as necessary, discussing with study physician. − Obtain neurology consult. − Consider hospitalization. − Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. − If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). − Once stable, gradually taper steroids over ≥28 days.

Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	**General Guidance**	**For Any Grade:** − The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. − Patients should be evaluated to rule out any alternative etiology (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, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. − It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1:** − Consider, as necessary, discussing with the study physician. − Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. − Obtain a neurology consult.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study	**For Grade 2:** − Consider, as necessary, discussing with the study physician. − Care should be taken to monitor patients for sentinel symptoms

	regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	of a potential decompensation as described above. − Obtain a neurology consult − Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or	**For Grade 3 or 4 (severe or life-threatening events):** − Consider, as necessary, discussing with study physician. − Recommend hospitalization. − Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting

		autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other

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

		and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start

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

[a]ASCO Educational Book 2015 “Managing Immune Checkpoint Blocking Antibody Side Effects” by Michael Postow MD.

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

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

Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	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 prior to subsequent doses. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

Non–Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	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	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the 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 Study Physician."

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