Investigational Drug	Durvalumab (MEDI4736)
AZ Study Number	ESR-18-13489; v4_12Nov18
HMRI Version Number	14.0
HMRI Date	September 10, 2024
IRB Number	Pro00020917
IND Number	Exempt

Multicenter Phase II Trial of Durvalumab (MEDI4736) with Trastuzumab and Pertuzumab Combination in HER2-Enriched and HER2-Amplified Breast Cancer (DTP Trial)

Sponsor: Houston Methodist Cancer Center and Houston Methodist Research Institute

PROTOCOL SYNOPSIS

Clinical Protocol

Study Title: Multicenter Phase II Trial of Durvalumab (MEDI4736) with Trastuzumab and Pertuzumab Combination in HER2-Enriched and HER2-Amplified Breast Cancer (DTP Trial)
Protocol Number: PRO00020917
Clinical Phase: II
Study Duration: 36 months

Study Treatment:

Durvalumab (MEDI4736) will be supplied as a 500-mg vial solution for infusion after dilution.

Trastuzumab is supplied as 420 mg multiple-dose or 150 mg single-dose vials for IV administration.
Pertuzumab is supplied as 420 mg/14 mL (30 mg/mL) single-dose vials for IV administration.

Research Hypothesis:

A more selected patient population with highly human epidermal growth factor receptor 2 (HER2)dependent breast cancer and the addition of durvalumab will increase the pathological response (pCR, RCB 0 and RCB 1) rate of neoadjuvant dual HER2 blockade (without chemotherapy).

Objectives:

Primary Objective:

1. Determination of the pathologic response rate [residual cancer burden (RCB)- 0, and RCB 1] in the breast of durvalumab with trastuzumab and pertuzumab combination in patients with HER2-enriched and HER2-amplified breast cancer.

Secondary Objectives:

1. Estimation of the RCB 0 and RCB 1 rate in the breast of durvalumab with trastuzumab and pertuzumab combination in patients whose tumors have <5% and ≥5% tumor-infiltrating lymphocytes (TILs).
2. Estimation of the RCB 0 and RCB 1 rate in the breast of durvalumab with trastuzumab and pertuzumab combination in patients with PD-L1−positive (≥1% tumor or stroma) and PD-L1−negative tumors (<1% tumor or stroma).
3. Determination of the 3-year disease-free survival (DFS) rate of durvalumab with trastuzumab and pertuzumab combination in patients with HER2-enriched and HER2-amplified breast cancer (only for patients who achieve RCB 0 and RCB 1).
4. Determination of the safety and toxicity of durvalumab with trastuzumab and pertuzumab combination in patients with HER2-enriched and HER2-amplified breast cancer, as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.

Exploratory Objective:

− Evaluation of the correlative molecular and genetic biomarkers of response and resistance to durvalumab with trastuzumab and pertuzumab combination in patients with HER2-enriched and HER2amplified breast cancer.

Study Design:

This is a multicenter Phase II study evaluating the efficacy and safety of durvalumab with trastuzumab and pertuzumab combination in patients with HER2-enriched and HER2-amplified breast cancer. The primary endpoint will be the RCB 0 and RCB 1 rate in the breast of durvalumab with trastuzumab and pertuzumab combination. The study will be conducted using a Simon's optimal two-stage design, and approximately 39 patients will be enrolled. Trastuzumab, pertuzumab, and durvalumab will be administered for 6 21-day cycles.

Patients will undergo breast MRI and biopsy after completion of 6 cycles of neoadjuvant therapy. Patients who have been determined based on biopsy to have achieved RCB 0 and RCB 1 will undergo surgery (within 30 days of the final dose of study treatment). Following surgery, RCB 0 and RCB 1 patients will continue to receive the combination of trastuzumab, pertuzumab, and durvalumab plus standard-of-care treatment to complete 1 year. Patients who have been determined based on biopsy to not have achieved RCB 0 and RCB 1 will undergo continued neoadjuvant treatment with targeted therapy and chemotherapy per physician's choice. Correlative studies will include tissue and blood-based molecular and genetic biomarkers of response and resistance to the regimen.

Number of Centers: 1

(1) Houston Methodist Hospital TMC

Number of Patients: 39

Study Population: Female patients aged ≥18 years with HER2-enriched and HER-amplified breast cancer.

Inclusion Criteria:

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol. Written informed consent and any locally required authorization (e.g., Health Insurance Portability and Accountability Act) will be obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

2. Female aged ≥18 years at the time of study entry.

3. Histologically confirmed HER2-enriched (by Mammaprint/BluePrint) and HER2-amplified (*ERBB2* mRNA >7.5-10)[57] HER2 overexpressing breast cancer.

4. Estrogen receptor (ER) and progesterone receptor negative (ER and progesterone receptor negativity are defined as ≤10% IHC staining).

5. Primary tumor greater than 1 cm diameter, measured by clinical examination and mammography or echography,

6. Any nodal status

7. Bilateral breast cancers that individually meet eligibility criteria are allowed.

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

9. Life expectancy ≥6 months.

10. Adequate organ and marrow function as defined below:

- Hemoglobin ≥10.0 g/dL with no blood transfusion in the past 28 days
- Absolute neutrophil count ≥1.5 × 10^9/L
- Platelet count ≥100 × 10^9/L
- Serum total bilirubin ≤1 × institutional upper limit of normal (ULN; In the case of known Gilbert's syndrome, a higher serum total bilirubin [< 1.5 × ULN] is allowed),
- Aspartate transaminase/alanine transaminase ≤2.5 × institutional ULN
- Alkaline phosphatase ≤1.5 × institutional ULN
- Creatinine ≤1.5 mg/dL

11. Baseline left ventricular ejection fraction ≥50%, as measured by multigated acquisition (MUGA) scan or echocardiogram (ECHO).

12. Evidence of postmenopausal status or negative serum pregnancy test for premenopausal patients. Negative serum β-human chorionic gonadotropin pregnancy test within 7 days prior to the first dose of study treatment for premenopausal patients. Women will be considered postmenopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

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

- Women ≥50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

13. Willing to provide biopsy tissues as required by the study.

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

Exclusion Criteria:

1. Participation in another clinical study with an investigational product within 28 days prior to the first dose of study treatment.

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.

3. Unresolved or unstable adverse events (AEs) from prior administration of another investigational drug.

4. Any concurrent chemotherapy, radiation therapy, immunotherapy, or biologic therapy for cancer treatment.

5. Major surgical procedure (as defined by the investigator) within 28 days prior to the first dose of study treatment.

6. History of allogeneic organ transplantation.

7. 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

8. History of active primary immunodeficiency.

9. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical exam and radiographic findings, and tuberculosis 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 hepatitis B surface antigen [HBsAg]) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

10. Current or prior use of immunosuppressive medication within 14 days prior to the first dose of study treatment. The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection)
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions

11. Receipt of live attenuated vaccine within 30 days prior to the first dose of study treatment. Note: Patients, if enrolled, should not receive live vaccine while receiving study treatment and up to 30 days after the last dose of study treatment.
12. Patients who are pregnant or breastfeeding or patients of reproductive potential who are not willing to employ effective birth control from screening to 7 months after the last dose of study treatment.
13. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
14. Patients with a mean QT interval of greater than or equal to 470ms calculated from 3 EKGs
15. Patients with underlying cardiovascular conditions that have recently undergone interventions including: cardiac ventricular arrhythmia requiring medication, history of second or third degree AV blocks, myocardial infarction with the previous year, congestive heart failure, and unstable angina
16. Patients with a LVEF less than 50%

Study Treatment, Dose and Mode of Administration:

Trastuzumab will be administered as 8 mg/kg IV loading dose, followed by 6 mg/kg IV every 3 weeks (Q3W). Pertuzumab will be administered as 840 mg IV loading dose, followed by 420 mg Q3W. Durvalumab will be administered at a fixed dose of 1120 mg IV Q3W.

Study Assessments and Criteria for Evaluation:

Safety Assessments:

AEs, physical exam, vital signs, ECOG performance status, electrocardiogram, MUGA acquisition scan or ECHO, hematology, clinical chemistry, and thyroid-stimulating hormone.

Efficacy Assessments:

Responders will be defined as having: 1.) pCR (RCB 0) and 2.) RCB 0 and 1.

Response will be analyzed according to TIL level (<5% vs. ≥5%) and programmed cell death-ligand 1 status (positive vs. negative)

3-year DFS rate will also be calculated.

Statistical Methods and Data Analysis:

This Phase II trial will be conducted using a Simon's minimax two-stage design. A null response rate of 35% is assumed.[16] The target response rate for the regimen will be 52%. When the probability of accepting a "bad" regimen (i.e., response rate ≤35%) is 0.10 (i.e., alpha) and the probability of rejecting a "good" regimen (i.e., response rate ≥52%) is 0.20 (i.e., beta or 1 – power), Simon's minimax design requires 15 patients in the first stage. If 4 or fewer patients respond to the regimen, the study will be stopped and the regimen will be declared as ineffective. If at least 5 of the first 15 patients respond, 24 additional patients will be entered on the study to reach a total of 39 patients. At the end of the second stage, the regimen will be rejected if the response rate is less than or equal to 17 out of 39 patients and will be accepted otherwise.

As a measure of safety, an initial cohort of 3 patients will be followed for toxicity through the first cycle of trastuzumab, pertuzumab, and durvalumab. If no more than 1 of 3 patients experience toxicity, then 3 more patients will be enrolled. If no more than 1 of 6 patients experience toxicity, then the study will be fully opened. Toxicity will be defined as any treatment-related death and any ≥ Grade 3 toxicity excluding alopecia and constitutional symptoms (as assessed by the NCI CTCAE v5). Additionally, toxicity after the first 6 patients will be monitored based on a beta-binomial model, assuming *a priori* that the probability of toxicity p is distributed beta (1, 1). Study accrual will be suspended and the safety profile of the combination will be reviewed by the safety monitoring committee if P_r ($p > .30$ | data) > 0.95. This stopping rule yields the following stopping bounds where the numerator represents the number of events needed to suspend accrual and the denominator represents the number treated at that point in the study: 7/12, 8/14, 9/17, 10/20, 11/22, 12/25, 13/28, 14/30, 15/33, and 16/36.

At the end of the study, the response rate and its associated 95% Wilson score confidence interval (CI) will be reported. The overall toxicity rate and CI will be reported, and the toxicity profile of the regimen will be summarized.

SCHEDULE OF STUDY ASSESSMENTS

			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6			EOT
			Week			Week			Week			Week			Week			Week			
Period	**Screening[a]**	**Baseline[b]**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	
Scheduling Window (days)	**-28 to -7**	**-7 to -1**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	
Informed Consent	X																				
Inclusion/Exclusion	X																				
Demographics	X																				
Medical History	X																				
Physical Exam[c]	X	X	X			X			X			X			X			X			X
ECOG Performance Status	X	X	X			X			X			X			X			X			X
12-Lead ECG[d]	X[q]							X													X
MUGA Scan or ECHO[d]	X							X													X
Hematology[e]	X	X	X			X			X			X			X			X			X
Clinical Chemistry[f]	X	X	X			X			X			X			X			X			X
TSH (reflex free T3 or free T4)[g]		X	X			X			X			X			X			X			X

SCHEDULE OF STUDY ASSESSMENTS

Period	Screening[a]	Baseline[b]	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6			EOT
			Week			Week			Week			Week			Week			Week			
			1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Scheduling Window (days)	**-28 to -7**	**-7 to -1**	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	
aPTT and INR[h]		X																			
Hepatitis B and C and HIV[i]	X																				
Serum Pregnancy (βhCG)[j]	X	X																			
Urinalysis[k]		X																			
Mammogram[l]		X								X											X
Breast Ultrasound[l]		X								X											X
Breast MRI[l]		X																			X
Biopsy[m]		X																			X
Blood Collection for Circulating DNA[n]		X						X													X
Trastuzumab[o]			X			X			X			X			X			X			
Pertuzumab[o]			X			X			X			X			X			X			

SCHEDULE OF STUDY ASSESSMENTS

Period	Screening[a]	Baseline[b]	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6			EOT
			Week			Week			Week			Week			Week			Week			
			1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Scheduling Window (days)	**-28 to -7**	**-7 to -1**	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	
Durvalumab[o]			X			X			X			X			X			X			
AEs and SAEs[p]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine transaminase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate transaminase; □-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; HIV = human immunodeficiency virus; INR = international normalized ratio; IV = intravenous; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; MUGA = multigated acquisition; pCR = pathological complete response; PD-L1 = programmed cell death-ligand 1; Q3W = every 3 weeks; RBC = red blood cell; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TB = total bilirubin; TIL = tumor-infiltrating lymphocyte; TSH = thyroid-stimulating hormone; WBC = white blood cell.

A window of ± 5 days is allowed for study visits and assessments/procedures (except as otherwise specified). Patients will undergo surgery within 30 days of the final dose of study treatment. EOT is defined as 7 to 10 days after the final dose of study treatment.

a. Within 28 days prior to the Cycle 1, Day 1 dose of trastuzumab, pertuzumab, and durvalumab.
b. Within 7 days prior to the Cycle 1, Day 1 dose of trastuzumab, pertuzumab, and durvalumab. Only screening procedures not performed within 7 days of dosing are required at baseline.
c. Physical exam will be performed at screening/baseline, before every cycle, and at EOT. Physical exam will include vital sign (blood pressure, respiratory rate, pulse, and oral or temporal temperature) and weight measurements. Height will be measured at screening only.

d. A 12-lead ECG and MUGA scan or ECHO will be performed at screening, after Cycle 2, at EOT, and when clinically indicated. The same method (MUGA scan or ECHO) must be used throughout the duration of the study. Twelve-lead ECG will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. Any clinically significant abnormalities detected require triplicate ECG results. Triplicate ECG will be performed at Screening and mean QT interval will be calculated.
e. Hematology assessments (hemoglobin, hematocrit, RBCs, platelets, MCH, MCHC, MCV, WBCs, absolute differential WBC count [neutrophils, lymphocytes, monocytes, eosinophils, and basophils], and ANC) will be performed at screening/baseline, before every cycle, at EOT, and when clinically indicated.
f. Clinical chemistry assessments (glucose, albumin, sodium, potassium, calcium, carbon dioxide, chloride, BUN, creatinine, TB, total protein, ALP, AST, ALT, magnesium, LDH, uric acid, and amylase) will be performed at screening/baseline, before every cycle, at EOT, and when clinically indicated.
g. TSH will be measured at baseline, before every cycle, at EOT, and when clinically indicated. If TSH is measured within 14 days prior to Cycle 1, Day 1, it does not need to be repeated at Cycle 1, Day 1. Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
h. aPTT and INR will be performed at baseline and when clinically indicated.
i. Hepatitis B and C and HIV testing will be performed at screening.
j. For women of childbearing potential, the results of a serum β-hCG pregnancy test must be negative within 7 days prior to the administration of the first dose of study treatment. If the screening serum β-hCG pregnancy test is performed more than 7 days before dosing, it must be repeated at baseline, with results known to be negative prior to the administration of the first dose of study treatment. β-hCG pregnancy testing is to be repeated as clinically indicated.
k. Urinalysis by dipstick will be performed at baseline and when clinically indicated.
l. Mammogram and breast ultrasound will be performed at baseline. Mammogram and breast ultrasound performed as standard of care can be used for baseline if performed within 90 days prior to the Cycle 1, Day 1 dose of trastuzumab, pertuzumab, and durvalumab. Mammogram and breast ultrasound will be repeated after Cycle 3 (+/- 3 days) and EOT. Breast MRI will be performed at baseline and EOT. Breast MRI performed as standard of care can be used for baseline if performed within 60 days prior to the Cycle 1, Day 1 dose of trastuzumab, pertuzumab, and durvalumab.
m. Tumor biopsy will be performed at baseline and EOT. Diagnostic biopsy may be used in lieu of repeat baseline biopsy, and collected for study purposes. Tissue will also be collected at the time of surgery. Banked tumor tissue obtained as part of the patient's standard of care and collected biopsy and surgical tissues will be used for determination of pathological response, PD-L1 expression, and TILs and correlative studies.
n. Blood samples for analysis of circulating DNA will be collected at baseline, after Cycle 2 (± 3 days), and at EOT and will be used for evaluation of correlative molecular and genetic biomarkers.
o. Trastuzumab, pertuzumab, and durvalumab will be administered for 6 21-day cycles (18 weeks). Trastuzumab, pertuzumab, and durvalumab will be administered sequentially as separate IV infusions on Day 1 at each cycle. Patients will be observed for 30−60 minutes after each

infusion. Trastuzumab will be the first infusion, followed by pertuzumab and then durvalumab. Trastuzumab will be administered as 8 mg/kg IV loading dose, followed by 6 mg/kg IV Q3W. Pertuzumab will be administered as 840 mg IV loading dose, followed by 420 mg IV Q3W. Durvalumab will be administered at a fixed dose of 1120 mg IV Q3W. Note: All assessments on infusion days are to be performed prior to infusion. Results of hematology and clinical chemistry results must be available before commencing an infusion. Patients who have been determined based on biopsy to have achieved pCR (RCB 0) or RCB 0 and 1 after completion of 6 cycles of neoadjuvant therapy will undergo surgery. Following surgery, RCB 0 and RCB 1 patients will continue to receive the trastuzumab, pertuzumab, and durvalumab (1120 mg Q3W) regimen plus standard-of-care treatment to complete 1 year. Follow-up will be provided every 12 weeks, as per standard-of-care, and will include physical exam, Echo, ECG, and labs (Clinical Chemistry, Hematology and TSH). Patients who have been determined based on biopsy to not have achieved p RCB 0 and RCB 1 after completion of 6 cycles of neoadjuvant therapy will undergo continued neoadjuvant treatment with targeted therapy and chemotherapy per physician's choice.

p. AEs and SAEs will be captured from the time of informed consent signing up to and including 30 days after the last treatment dose.

q. Triplicate ECG will be performed at Screening and mean QT interval will be calculated.

Contents

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
Anti-HBc	Hepatitis B core antibody
AST	Aspartate transaminase
β-hCG	Beta-human chorionic gonadotropin
BUN	Blood urea nitrogen
CI	Confidence interval
CRF	Case report form
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
DFS	Disease-free survival
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EOT	End of treatment

ER	Estrogen receptor
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen

Abbreviation or special term	**Explanation**
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HR	Hormone receptor
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonization
IHC	Immunohistochemical
ILD	Interstitial lung disease
imAE	Immune-mediated adverse event
IRB	Institutional review board
IV	Intravenous(ly)
LDH	Lactate dehydrogenase
LH	Luteinizing hormone

LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
pCR	Pathological complete response

Abbreviation or special term	**Explanation**
PD	Progressive disease
PD-1	Programmed cell death-1
PD-L1	Programmed cell death-ligand 1
PD-L2	Programmed cell death-ligand 2
PI3KCA	Phosphatidylinositol-4,5-bisphosphonate 3-kinase catalytic subunit alpha
PK	Pharmacokinetic(s)
PTEN	Phosphatase and tensin homolog
Q2W	Every 2 weeks

Q3W	Every 3 weeks
QD	Once daily
RBC	Red blood cell
SAE	Serious adverse event
TB	Total bilirubin
TIL	Tumor-infiltrating lymphocyte
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
U.S.	United States
WBC	White blood cell

1 BACKGROUND

1.1 Human epidermal growth factor receptor 2 and breast cancer

Human epidermal growth factor receptor 2 (HER2) amplification or overexpression occurs in approximately 20–25% of breast cancers. HER2 is a tyrosine kinase receptor belonging to the HER family that also includes epidermal growth factor receptor (EGFR; HER1), HER3, and HER4. HER2 is activated by either heterodimerization with other ligand-bound HER family members or, when overexpressed, by ligand-independent homodimerization. HER2 functions as a driver oncogene in HER2-overexpressing tumors.[1,2] HER2 overexpression is associated with aggressive disease, relatively poor prognosis, and worse clinical outcomes.

1.2 Neoadjuvant therapy for HER2-positive breast cancer

Neoadjuvant therapy is standard of care for patients with locally advanced, inflammatory, or inoperable primary breast cancer. Neoadjuvant therapy is used to downstage tumors, thereby potentially rendering them suitable for breast-conserving surgery. Clinical studies have shown that pathological complete response (pCR) to neoadjuvant therapy is strongly correlated with survival and prognosis in breast cancer patients.[3-5] Breast cancer patients who achieve pCR to neoadjuvant therapy, particularly those with HER2-positive breast cancers, are known to have better disease-free survival (DFS) and overall survival compared with those with residual disease.[6-8] The addition of the anti-HER2 monoclonal antibody (mAb) trastuzumab to neoadjuvant chemotherapy has been shown to improve pCR rate in patients with HER2-positive locally advanced breast cancer.[9-11] Because of the complex and redundant signaling pathways of the HER family, dual anti-HER2 therapies have been developed to more completely block signaling from HER2 and its related HER family members. Multiple large randomized clinical trials have demonstrated that dual HER2-targeted therapies are synergistic and result in improved efficacy.

Dual HER2 blockade with trastuzumab and pertuzumab in combination with taxane-based chemotherapy is the current neoadjuvant approach for patients with HER2-positive breast cancer. Pertuzumab is an anti-HER2 mAb that targets the extracellular dimerization domain of HER2 to block ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4. The multicenter, open-label, randomized Phase II NeoSphere study (NCT00545688) demonstrated that combining neoadjuvant trastuzumab and docetaxel with pertuzumab significantly improved pCR rate compared with trastuzumab plus docetaxel, pertuzumab plus docetaxel, and trastuzumab and pertuzumab in patients with locally advanced, inflammatory, or early HER2-positive breast cancer (45.8% vs. 29%, 24%, and 16.8%, respectively).[12] However, not all HER2-positive breast cancers respond to HER2targeted therapy and many that initially respond later develop resistance. Therefore, novel strategies are needed to overcome this intrinsic/acquired resistance.

1.2.1 HER2 enriched breast tumor subtype and response to HER2 dual blockade without chemotherapy

The potential of using dual HER2 blockade without chemotherapy in the treatment of HER2positive breast cancer has been demonstrated in several clinical studies. Development of such chemotherapy-free regimens would be of particular importance for patients who are unable to tolerate cytotoxic drugs and would spare a subset of patients the short and long-term toxicities associated with cytotoxic-based therapy. In the trastuzumab and pertuzumab without chemotherapy arm of the NeoSphere study, 16.8% (18/107) of patients achieved pCR after 12 weeks of neoadjuvant treatment.[12] We conducted a multicenter Phase II study of neoadjuvant lapatinib and trastuzumab with hormonal therapy and without chemotherapy in patients with HER2-overexpressing breast cancer.[13] Patients received trastuzumab (4 mg/kg intravenous [IV] loading dose, followed by 2 mg/kg every 3 weeks [Q3W]) and lapatinib (1000 mg orally once daily [QD]) for 12 weeks. Patients with estrogen receptor (ER)-positive tumors also received letrozole. Sixty-four patients were evaluable for response. The overall pCR rate (i.e., absence of all invasive cancer) was 53% (34/64). The pCR rate was 40% (10/25) in the ER-negative cohort and 21% (8/39) in the ER-positive cohort. In the multicenter, randomized Phase II UK EPHOS-B study (NCT01104571), 127 patients with newly diagnosed HER2-positive breast cancer were randomized to receive no treatment (control group; n = 29), trastuzumab only (n = 32), or trastuzumab and lapatinib in combination (n = 66) for 11 days before surgery.[14] Of the 66 patients treated with the trastuzumab and lapatinib combination, 7 (10.6%) had their tumors disappear (pCR) and 11 (16.7%) had minimal residual disease (<5 mm invasive tumor). In contrast, none of the patients in the control and trastuzumab only groups achieved pCR and none of the patients in the control group and 1 patient in the trastuzumab only group had minimal residual disease. Together, these findings suggest that a proportion of HER2-positive tumors are responsive to HER2-targeted combination therapies alone. Importantly, results of the nonrandomized, open-label Phase II PAMELA study (NCT01973660) indicated that the PAM50 HER2-enriched subtype is a strong predictor of sensitivity to dual HER2 blockade without chemotherapy in patients with HER2-positive early breast cancer.[15] Patients (n = 151) were treated with dual HER2 blockade consisting of lapatinib (1000 mg QD) and trastuzumab (6 mg/kg Q3W) for 18 weeks. Hormone receptor (HR)-positive patients also received endocrine therapy (letrozole or tamoxifen). pCR rate was significantly higher in patients with HER2enriched tumors compared with those with non-HER2-enriched tumors (40.6% vs. 10.0%; p = 0.0004). Furthermore, pCR rate was 43.1% in patients with HR-negative disease and 18.2% in those with HR-positive disease (p = 0038). Combined HER2-enriched subtype/ERBB2-high mRNA level was shown to be a strong predictor of pCR following dual HER2 blockade without chemotherapy; pCR rates in HER2-enriched/ERBB2-high, non-HER2-enriched/ERBB2-high,

HER2-enriched/ERBB2-low, and non-HER2-enriched/ERBB2-low groups were 45.0%, 16.1%, 10.8%, and 6.7%, respectively.[16,17]

1.3 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.[18]

Programmed cell death-ligand 1 (PD-L1) is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The programmed cell death-1 (PD-1) receptor (CD279) is expressed on the surface of activated T-cells.[19] It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273).[20] PD-1 and PD-L1/PD-L2 belong to the family of immune checkpoint proteins that act as coinhibitory factors, which can halt or limit the development of T-cell responses. 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.[21] Importantly, PD-L1 is commonly overexpressed on tumor cells or on non-transformed cells in the tumor microenvironment.[22] PD-L1 expressed on the tumor cells binds to PD-1 on 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 antitumor 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 PD-L1 inhibits the interaction of PD-L1 with 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 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,[20,23-27]with responses that tend to be more pronounced in patients with PD-L1–expressing tumors.[28-30] In addition, high mutational burden (e.g., in bladder carcinoma[31]) may contribute to the responses seen with immunotherapy.

Preclinical data have now been added to a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) and PD-L1 has promising clinical activity. The anti–CTLA-4 agent ipilimumab was granted United States (U.S.) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies, whereas

nivolumab and pembrolizumab, two anti–PD-1 agents, and atezolizumab, an anti–PD-L1 agent, have been granted approvals by agencies such as the U.S. FDA and European Medicines Agency for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small cell lung cancer (NSCLC) and urothelial carcinoma. In addition, there are data from agents in the anti–PD-1/PD-L1 class showing clinical activity in a wide range of tumor types.

1.4 Durvalumab (MEDI4736)

Durvalumab (MEDI4736) is a human mAb of the immunoglobulin G1 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). Durvalumab is approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy, or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Durvalumab is also approved for the treatment of patients with unresectable, Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

1.4.1 Durvalumab non-clinical and clinical experience

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

The proposed mechanism of action 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 interferon-γ.[32] *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell−dependent mechanism.[32] 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.

To date, durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 1.7.2.1. Refer to the current durvalumab IB for a complete summary of non-clinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

1.5 Research hypothesis

A more selected patient population with highly HER2-dependent breast cancer and the addition of durvalumab will increase the pCR rate of neoadjuvant dual HER2 blockade with trastuzumab and pertuzumab (without chemotherapy).

1.6 Rationale for conducting this study

Clinical studies have demonstrated the superiority of dual HER2 blockade over single-agent blockade in achieving a more comprehensive inhibition of the various HER2 dimers. Despite the efficacy of dual HER2 blockade, many HER2-positive breast cancers fail to respond and those that initially respond eventually develop resistance. As *de novo* and acquired resistance still remain a significant clinical challenge, novel combination strategies are needed to overcome resistance.

Clinical studies have indicated the potential of using dual HER2 blockade without chemotherapy in the treatment of HER2-positive breast cancer, particularly HER2-enriched and HER2-amplified breast cancer (see Section 1.2.1 − HER2-enriched breast tumor subtype and response to HER2 dual blockade without chemotherapy).[12-17] As several studies have indicated the relevance of the immune system in the response to HER2-targeted therapy, dual HER2 blockade in combination with immunotherapy may represent a valid approach. In addition to direct binding to HER2, trastuzumab and pertuzumab also induce antibody-dependent cellmediated cytotoxicity (ADCC) through the interaction of the Fc portion of trastuzumab/pertuzumab with Fcγ receptors on immune cells.[33,34] ADCC has been linked to the *in vitro*/*in vivo* and clinical responses to trastuzumab.[35-41] Notably, the HER2-enriched subtype of HER2-positive breast cancer has been shown to have the highest rate of immune response to trastuzumab treatment.[42] HER2-positive breast tumors have also been shown to contain high levels of tumor-infiltrating lymphocytes (TILs) and this has been shown to be associated with increased pCR rates to neoadjuvant HER2-targeted therapy.[43-46]

Resistance to HER2-targeted therapy *in vitro* has been correlated with increased PD-L1 expression.[47] In the NeoSphere trial, *PD-L1* expression was associated with a lower pCR rate to trastuzumab and pertuzumab (odds ratio = 0.30; 95% confidence interval [CI]: 0.15–0.61; p = 0.0007).[48] Intratumoral CD8+ T-cells were found to be significantly associated with pCR to anti-HER2 neoadjuvant therapy in patients with HER2-positive breast cancer.[49] Furthermore, all patients with intratumoral CD8+ T-cells and no PD-L1 expression (tumor/immune cells) achieved pCR. The efficacy of combined HER2 and PD-1 targeting in HER2-positive breast cancer has been demonstrated in the metastatic setting. In the Phase Ib/II PANACEA trial (KEYNOTE-014; NCT02129556), the combination of trastuzumab and pembrolizumab achieved an overall response rate of 15.2% and a disease control rate of 24% in 58 patients with trastuzumab-resistant metastatic breast cancer.[50] Together, these studies indicate the contribution of the immune system in the response/resistance to HER2-targeted therapies. Given the involvement of PD-L1 in the resistance to HER2-targeted therapy, PD-L1 blockade may offer a rational approach to circumvent the resistance to and improve the efficacy of HER2targeted therapy.

1.6.1 Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data from a Phase I study in patients with solid tumors (Study 1108; n = 292; doses = 0.1 to 10 mg/kg every 2 weeks

[Q2W] or 15 mg/kg Q3W). Population PK analysis indicated only minor impact of body weight on the 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-patient variability with the fixed dosing regimen.

Similar findings have been reported by others.[51-54] 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.[52] 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 betweenpatient variability in PK/pharmacodynamics parameters.[53]

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given the expectation of similar PK exposure and variability, we considered it feasible to switch to fixed dosing regimens.

1.6.2 Rationale for Q3W dosing

The planned dose of trastuzumab for this study is 8 mg/kg IV loading dose, followed by 6 mg/kg IV Q3W. The planned dose of pertuzumab is 840 mg IV loading dose, followed by 420 mg IV Q3W. These are the approved doses for the neoadjuvant treatment of HER2-positive breast cancer. Given that trastuzumab and pertuzumab should be dosed Q3W, Q3W dosing will also be used for durvalumab. The planned dose of durvalumab for this study is 1120 mg IV Q3W.

1.7 Benefit/risk and ethical assessment

1.7.1 Potential benefits

Preclinical and clinical data have demonstrated a role of PD-L1 in the resistance to HER2targeted therapy[39-41] and therefore, PD-L1 blockade could be an effective strategy to overcome treatment resistance. HER2-enriched tumors with HER2 amplification have been found to benefit most from anti-HER2 therapy and to elicit a strong immune response to anti-HER2 therapy.[38] Addition of durvalumab may potentiate the immune response to neoadjuvant trastuzumab and pertuzumab, leading to better treatment outcomes (i.e., pCR). This is highly significant given the association of pCR with long-term survival in HER2-positive patients.

The impact of PD-L1 status and TILs on response (pCR) to the durvalumab with trastuzumab and pertuzumab combination will be assessed. Furthermore, biopsied tumor tissues and blood samples (circulating DNA) will be evaluated for molecular and genetic biomarkers of response and resistance to durvalumab with trastuzumab and pertuzumab combination. Together, this

information will be important in identifying patients most likely to benefit from the durvalumab with trastuzumab and pertuzumab combination.

1.7.2 Overall risks

mAbs directed against immune checkpoint proteins, such as PD-L1 and PD-1, aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system, however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune-mediated effects can occur in nearly any organ system and are most commonly seen as gastrointestinal adverse events (AEs) such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis, and endocrinopathies including hypothyroidism and hyperthyroidism.

1.7.2.1 Durvalumab

Risks with durvalumab include, but are not limited to, diarrhea/colitis and intestinal perforation, pneumonitis/ILD, endocrinopathies (hypothyroidism and hyperthyroidism, type I diabetes mellitus(which may present as diabetic ketoacidosis), Diabetes insipidus, hypophysitis, and adrenal insufficiency), hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, (including pemphigoid), myocarditis, Encephalitis, myositis/polymyositis, Immune thrombocytopenia, non-infective encephalitis, cytokine release syndrome , uveitis, and immune-mediated arthritis. Other rare or less frequent inflammatory events including neurotoxicities, neuromuscular toxicities (e.g., Guillain-Barré syndrome, myasthenia gravis), infusion-related reactions, subcutaneouss injection site reaction, hypersensitivity reactions, and infections/serious infections.

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

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

In monotherapy clinical studies, 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 a serious AE (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 AEs (imAEs; Appendix 1).

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

1.7.3 Overall benefit-risk

Durvalumab has shown significant activity and manageable toxicity in urothelial carcinoma and NSCLC. Durvalumab in combination with chemotherapy has also shown promising efficacy in the neoadjuvant setting in triple negative breast cancer. Preliminary results of a Phase I/II neoadjuvant study (NCT02489448) showed that the addition of durvalumab to chemotherapy (weekly nab-paclitaxel followed by dose-dense doxorubicin and cyclophosphamide) increased pCR rate (71% [5/7 patients]) compared with the historical rate of 35−40% with chemotherapy alone.[55]

Phase I study data showed that there were no dose-limiting toxicities with the combination of durvalumab (1120 mg IV Q3W) and trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg IV Q3W) in patients with HER2-positive metastatic breast cancer, and the recommended Phase 2 dose was the standard full doses of both agents.[56]

The study will be conducted using a Simon's optimal two-stage design. This design allows for early study termination for futility and therefore, minimizes the number of patients exposed to an intervention that is probably ineffective.

2 OBJECTIVES

2.1 Primary objective

1. Determination of pathologic response (pCR (RCB 0) and RCB 1) rate in the breast of durvalumab with trastuzumab and pertuzumab combination in patients with HER2-enriched and HER2-amplified breast cancer.

2.2 Secondary objectives

1. Estimation of the RCB 0 and RCB 1 rate in the breast of durvalumab with trastuzumab and pertuzumab combination in patients whose tumors have <5% and ≥5% TILs.

2. Estimation of the RCB 0 and RCB 1 rate in the breast of durvalumab with trastuzumab and pertuzumab combination in patients with PD-L1−positive (≥1% tumor or stroma) and PDL1−negative tumors (<1% tumor or stroma).

3. Determination of the 3-year DFS rate of durvalumab with trastuzumab and pertuzumab combination in patients with HER2-enriched and HER2-amplified breast cancer (only for patients who achieve RCB 0 and RCB1).

4. Determination of the safety and toxicity of durvalumab with trastuzumab and pertuzumab combination in patients with HER2-enriched and HER2-amplified breast cancer, as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.

2.3 Exploratory objective

1. Evaluation of the correlative molecular and genetic biomarkers of response and resistance to durvalumab with trastuzumab and pertuzumab combination in patients with HER2-enriched and HER2-amplified breast cancer, including but not limited to phosphatidylinositol-4,5bisphosphate 3-kinase catalytic subunit alpha (PI3KCA) and phosphatase and tensin homolog (PTEN).

3 ENDPOINTS

3.1 Primary endpoint

1. Pathologic response (RCB 0 and RCB 1) rate in the breast of durvalumab with trastuzumab and pertuzumab combination in patients with HER2-enriched and HER2-amplified breast cancer.

3.2 Secondary endpoints

1. Pathologic response (RCB 0 and RCB 1) rate in the breast of durvalumab with trastuzumab and pertuzumab combination in patients whose tumors have <5% and ≥5% TILs.

2. Pathologic response (RCB 0 and RCB 1) rate in the breast of durvalumab with trastuzumab and pertuzumab combination in patients with PD-L1−positive (≥1% tumor or stroma) and PDL1−negative tumors (<1% tumor or stroma).

3. Three-year DFS rate of durvalumab with trastuzumab and pertuzumab combination in patients with HER2-enriched and HER2-amplified breast cancer (only for patients who achieve RCB 0 and RCB 1). DFS will be calculated from the date of surgery to the date of first event (second primary cancer, locoregional relapse, distant relapse, or death from any cause).

4. Safety and toxicity of durvalumab with trastuzumab and pertuzumab combination in patients with HER2-enriched and HER2-amplified breast cancer, as assessed by the NCI CTCAE v5. Toxicity will be defined as any treatment-related death or any ≥ Grade 3 AE excluding alopecia and constitutional symptoms.

3.3 Exploratory endpoint

1 Correlative molecular and genetic biomarkers of response and resistance to durvalumab with trastuzumab and pertuzumab combination in patients with HER2-enriched and HER2-amplified breast cancer, including but not limited to PI3KCA and PTEN. If sufficient tissue is available, next-generation sequencing will be done to identify potential molecular correlates of the treatment regimen.

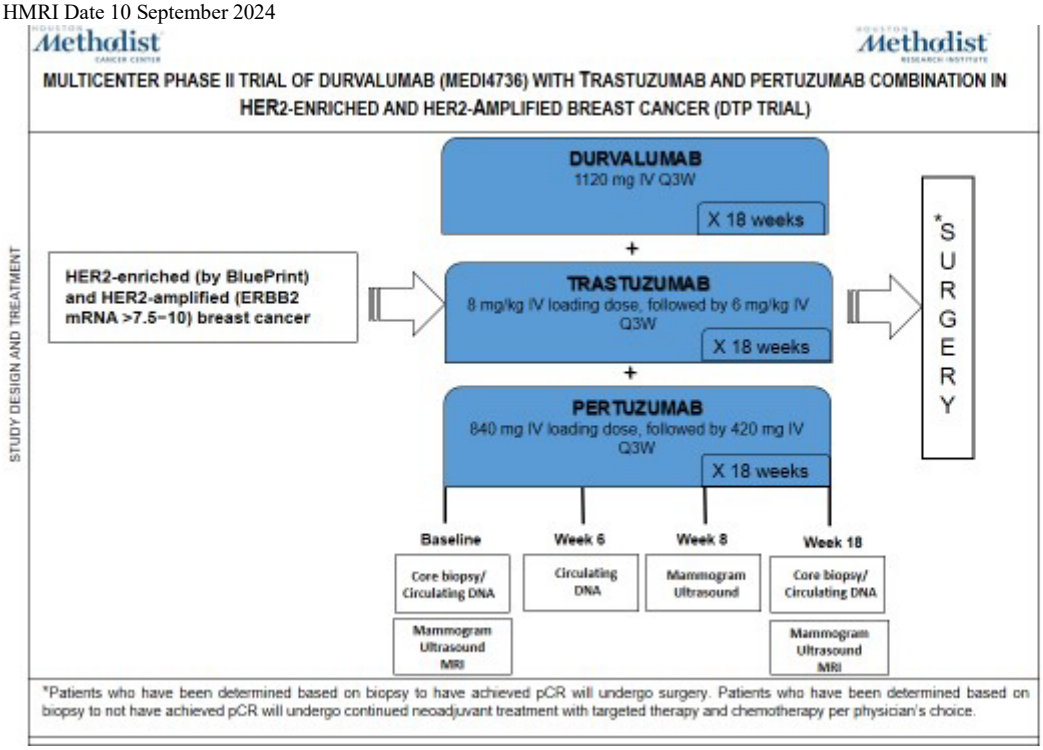
4 STUDY DESIGN

4.1 Overview of study design

This is a multicenter Phase II study evaluating the efficacy and safety of durvalumab with trastuzumab and pertuzumab combination in patients with HER2-enriched and HER2-amplified breast cancer. The primary endpoint will be the pathologic response rate (RCB 0 and RCB 1) rate in the breast of the regimen. The study will be conducted using a Simon's minimax twostage design, and approximately 39 patients will be enrolled. Trastuzumab, pertuzumab, and durvalumab will be administered for 6 21-day cycles. Patients will undergo breast MRI and biopsy after completion of 6 cycles of neoadjuvant therapy. Patients who have been determined based on biopsy to have achieved pathologic response (RCB 0 and RCB 1) will undergo surgery (within 30 days of the final dose of study treatment). Following surgery, RCB 0 and RCB 1 patients will continue to receive the combination of trastuzumab, pertuzumab, and durvalumab plus standard-of-care treatment to complete 1 year. Patients who have been determined based on biopsy to not have achieved RCB 0 and RCB 1 will undergo continued neoadjuvant treatment with targeted therapy and chemotherapy per physician's choice. Correlative studies will include tissue and blood-based molecular and genetic biomarkers of response and resistance to the regimen.

4.2 Study schema

Figure 1.



5 PATIENT SELECTION

5.1 Inclusion criteria

For inclusion in the study, patients must fulfill all of the following criteria:

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (e.g., Health Insurance Portability and Accountability Act) will be obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

2. Female aged ≥18 years at the time of study entry.

3. Histologically confirmed HER2-enriched (by Mammaprint/BluePrint) and HER2-amplified (*ERBB2* mRNA >7.5-10)[57] HER2 overexpressing breast cancer.

4. ER and progesterone receptor negative (ER and progesterone receptor negativity are defined as ≤10% IHC staining).

5. Primary tumor greater than 1 cm diameter, measured by clinical examination and mammography or echography.
6. Any nodal status.
7. Bilateral breast cancers that individually meet eligibility criteria are allowed.

8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix 2).

9. Life expectancy ≥6 months.

10. Adequate organ and marrow function as defined below:

    - Hemoglobin ≥10.0 g/dL with no blood transfusion in the past 28 days
    - Absolute neutrophil count (ANC) ≥1.5 × 10^9/L
    - Platelet count ≥100 × 10^9/L
    - Serum total bilirubin (TB) ≤1 × institutional upper limit of normal (ULN; In the case of known Gilbert's syndrome, a higher serum TB [<1.5 × ULN] is allowed),
    - Aspartate transaminase (AST)/alanine transaminase (ALT) ≤2.5 × institutional ULN
    - Alkaline phosphatase (ALP) ≤1.5 × institutional ULN
    - Creatinine ≤1.5 mg/dL

11. Baseline left ventricular ejection fraction (LVEF) ≥50%, as measured by multigated acquisition (MUGA) scan or echocardiogram (ECHO).

12. Evidence of postmenopausal status or negative serum pregnancy test for premenopausal patients. Negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test within 7 days prior to the first dose of study treatment for premenopausal patients. Women will be considered postmenopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

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

- Women ≥50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

13. Willing to provide biopsy tissues as required by the study.

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

5.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Participation in another clinical study with an investigational product within 28 days prior to the first dose of study treatment.

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.

3. Unresolved or unstable AEs from prior administration of another investigational drug.

4. Any concurrent chemotherapy, radiation therapy, immunotherapy, or biologic therapy for cancer treatment.

5. Major surgical procedure (as defined by the investigator) within 28 days prior to the first dose of study treatment.

6. History of allogeneic organ transplantation.

7. 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

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

9. History of another primary malignancy except for:

   - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study treatment and of low potential risk for recurrence
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
   - Adequately treated carcinoma in situ without evidence of disease.

10. History of active primary immunodeficiency.

11. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical exam and radiographic findings, and tuberculosis 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 hepatitis B surface antigen [HBsAg]) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

12. Current or prior use of immunosuppressive medication within 14 days prior to the first dose of study treatment. The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intraarticular injection)
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions

13. Receipt of live attenuated vaccine within 30 days prior to the first dose of study treatment. Note: Patients, if enrolled, should not receive live vaccine while receiving study treatment and up to 30 days after the last dose of study treatment.

14. Patients who are pregnant or breastfeeding or patients of reproductive potential who are not willing to employ effective birth control from screening to 7 months after the last dose of study treatment.

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

16. Patients with a measurement of the mean QT interval of greater or equal to 470ms calculated from 3 EKGs

17. Patients who have underlying cardiovascular conditions that have recently undergone interventions including: cardiac ventricular arrhythmia requiring medication, history of second or third degree AV blocks, myocardial infarction within the previous year, congestive heart failure, and unstable angina

18. Patients with a LVEF less than 50%

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 5.3.

5.3 Withdrawal of patients from study treatment and/or study

5.3.1 Permanent discontinuation of study treatment

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

1. Patient or legal representative withdraws consent

2. Lost to follow-up

3. AE that, in the opinion of the investigator or 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. Patients who fail to meet the selection criteria should not be enrolled. When patients who do not meet the selection criteria in error or incorrectly started on study treatment, or where patients subsequently fail to meet the study criteria post-initiation, the patient should have their study treatment stopped and be withdrawn from the study.

5. Confirmed positive serum (β-hCG) pregnancy test or intent to become pregnant

6. Any AE that meets criteria for discontinuation as defined in Section 6.3 and Appendix 1

7. Dose interruption that exceeds 3 weeks

8. Grade ≥3 infusion reaction

9. Patient non-compliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits

10. Initiation of alternative anticancer therapy including another investigational agent

11. Confirmed radiographic disease progression and investigator determination that the patient is no longer benefiting from the study treatment

When a patient is permanently discontinued from receiving the study treatment prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of withdrawal. The patient will continue to be followed for safety unless consent is withdrawn or the patient is lost to follow-up or enrolled in another clinical study.

5.3.2 Withdrawal of consent

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

Patients who withdraw consent for further participation in the study will not receive any further study treatment or further study observation. 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.

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

- An AE that, in the opinion of the investigator or AstraZeneca, contraindicates further dosing
- Pregnancy or intent to become pregnant
- Non-compliance with the study protocol that, in the opinion of the investigator or AstraZeneca, warrants withdrawal from study treatment (e.g., refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent
- Clinical progression, i.e. investigator determination that the patient is no longer benefiting from the study treatment, with or without radiographic progression
- Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (Appendix 1)

6 STUDY TREATMENT

6.1 Dosing and administration

Trastuzumab, pertuzumab, and durvalumab (MEDI4736) will be given for 6 cycles unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Cycle length will be 21 days. Trastuzumab, pertuzumab, and durvalumab will be administered sequentially as separate IV infusions on Day 1 at each cycle. Trastuzumab will be the first infusion, followed by pertuzumab and then durvalumab. Patients will be observed for 30-60 minutes after each infusion.

Trastuzumab:

- Loading dose as 8 mg/kg IV infusion over 90 minutes
- Subsequent doses as 6 mg/kg IV infusion over 30–90 minutes Q3W Pertuzumab:

- Loading dose as 840 mg IV infusion over 60 minutes
- Subsequent doses as 420 mg IV infusion over 30–60 minutes Q3W

Durvalumab: 1120 mg IV infusion over 60 minutes Q3W

Results of hematology and clinical chemistry results must be available before commencing an infusion.

Patients will undergo breast MRI and biopsy after completion of 6 cycles of neoadjuvant therapy. Patients who have been determined based on biopsy to have achieved RCB 0 and RCB 1 will undergo surgery (within 30 days of the final dose of study treatment). Following surgery, RCB 0 and RCB 1 patients will continue to receive the trastuzumab, pertuzumab, and durvalumab (1120 mg Q3W) regimen plus standard-of-care treatment to complete 1 year. Patients who have been determined based on biopsy to not have achieved RCB 0 and RCB 1will undergo continued neoadjuvant treatment with targeted therapy and chemotherapy per physician's choice.

6.2 Durvalumab

6.2.1 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 and a density of 1.054 g/mL. 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 original packaging until use to prevent prolonged light exposure.

6.2.2 Preparation

6.2.2.1 Preparation of durvalumab doses for administration with an IV bag

The dose of durvalumab (MEDI4736) for administration must be prepared using aseptic technique. Total time from needle puncture of the durvalumab (MEDI4736) vial to the start of administration should not exceed:

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

A dose of 1120 mg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 22.4 mL of durvalumab (MEDI4736) (i.e., 1120 mg 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 coadminister 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.

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.

6.2.3 Monitoring of dose administration

Patients will be monitored before, during, and after the infusion (30-60 minutes).

In the event of a ≤ Grade 2 infusion-related reaction, the infusion rate of durvalumab may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. 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, durvalumab will be discontinued. The standard infusion time is 1 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 Dosing Modification and Toxicity Management Guidelines in Appendix 1.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

6.2.4 Accountability and dispensation

The study drug provided for this study (durvalumab) is for use as directed in the study protocol. It is the investigator's/institution's responsibility to establish a system for handling investigational products so as to ensure that:

- Deliveries of such products from AstraZeneca are correctly received by a responsible person
- Such deliveries are recorded
- Such products are handled and stored safely and properly as stated on the label
- Such products are only dispensed to study patients in accordance with the protocol

The investigational staff will account for investigational product dispensed and returned.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include identification of the person to whom the investigational product was dispensed, the quantity and date of dispensing and unused investigational product returned to the investigator. This record is in addition to any drug accountability information recorded on the case report form (CRF). Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the investigator or qualified designee or a pharmacist.

6.3 Toxicity management guidelines

Any toxicity observed during the course of the study can be managed by interruption of the dose of study treatment. **Dose reductions for trastuzumab, pertuzumab, and durvalumab are not permitted.** Repeat dose interruptions are allowed as required, for a maximum of 3 weeks on each occasion. If an interruption of longer than 3 weeks is required, the patient should be withdrawn. When a patient withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed as described in Section 8.1.4.1.

6.3.1 Durvalumab

Guidelines for the management of imAEs, infusion-related reactions, and non-imAEs for durvalumab are provided in the durvalumab Dosing Modification and Toxicity Management Guidelines in Appendix 1. The most current version of the durvalumab Toxicity Management Guidelines is also available through the following link: https://tmg.azirae.com.

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

In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see Dosing Modification and Toxicity Management Guidelines in Appendix 1).

Following the first dose, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines in Appendix 1. These guidelines apply to AEs considered causally related to durvalumab by the reporting investigator.
All toxicities will be graded according to the NCI CTCAE v5.

6.3.2 Trastuzumab and pertuzumab

Left ventricular dysfunction

Trastuzumab and pertuzumab can result in subclinical and clinical cardiac failure manifesting as decreased LVEF and congestive heart failure. Dose modifications for left ventricular dysfunction are shown in Table 1.

Table 1: Dose Modifications for Left Ventricular Dysfunction

Withhold trastuzumab and pertuzumab for an LVEF decrease to:		Resume trastuzumab and pertuzumab if LVEF has recovered to:	
Either		Either	
<40%	40−45% with a fall of ≥10% points below pretreatment value	>45%	40−45% with a fall of <10% points below pretreatment value
<50% with a fall of ≥10% points below		Either	
pretreatment value		≥50%	<10% points below pretreatment value

LVEF = left ventricular ejection fraction.

Infusion-related reactions

Pertuzumab administration can result in infusion-related reactions. Common reactions include pyrexia, chills, fatigue, headache, hypersensitivity, asthenia, and vomiting. The majority of reactions are Grade 1 or 2, with less than 1% being Grade 3 or 4.

- Decrease the rate of infusion for mild or moderate infusion reactions
- Interrupt the infusion in patients with dyspnea or clinically significant hypotension
- Discontinue infusion for severe or life-threatening infusion reactions

Trastuzumab administration can result in serious and fatal infusion-related reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of trastuzumab administration.

- Interrupt infusion for dyspnea or clinically significant hypotension
- Discontinue infusion for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.

7 Restrictions during the study and concomitant treatment(s)

7.1 Restrictions during the study

7.1.1 Contraception

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

Female patient of childbearing potential

- Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Table 2) from the time of screening throughout the total duration of the study treatment and 7 months after the last dose of study treatment. Non-sterilized male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or postmenopausal.

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

- Women <50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have LH and FSH levels in the postmenopausal range for the institution.
- Women ≥50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

Highly effective methods of contraception, defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are described in Table 2. Note that some contraception methods are not considered highly effective (e.g., male or female condom

with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 2: Highly Effective Methods of Contraception (<1% Failure Rate)

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

[a]This is also considered a hormonal method.

Blood donation
Patients should not donate blood while participating in this study and for 3 months after the last dose of study treatment.

7.2 Concomitant treatment(s)

All medications that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded in the CRF including all prescription, over-the-counter, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date may also be included in the CRF.

All concomitant medications received within 28 days before the first dose of study treatment and 30 days after the last dose of study treatment should be recorded. All concomitant medications should be recorded in the CRF including supportive care drugs and the drugs used to treat AEs or chronic diseases as well as non-drug supportive interventions. The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the CRF.

7.2.1 Permitted concomitant medications

Table 3: Supportive Medications

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management)	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

7.2.2 Prohibited concomitant medications

Table 4: Prohibited Concomitant Medications

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment
Any concurrent chemotherapy, immunotherapy, or biologic therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment.

Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly or used for premedication prior to durvalumab infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study treatment-related AEs • Short-term premedication for prophylaxis of trastuzumab/pertuzumab hypersensitivity reactions • Use in patients with contrast allergies • Use of inhaled, topical, and intranasal corticosteroids *A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of* non−immunotherapy-related events experienced by *the patient (e.g., chronic obstructive pulmonary disease, nausea, etc).*
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Live attenuated vaccines	Should not be given through 30 days after the last dose of study treatment
Herbal and natural remedies that may have immune-modulating effects	Should not be given concomitantly
EGFR TKI = epidermal growth factor receptor tyrosine kinase inhibitor; mAb = monoclonal antibody.	

8 STUDY PROCEDURES

8.1 Schedule of study procedures

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedule of Assessments during screening/baseline, treatment, and end of treatment (EOT) phases is provided following the Protocol Synopsis.

8.1.1 Screening phase

Screening procedures will be performed up to 28 days before Cycle 1, Day 1. All patients must first read, understand, and sign the institutional review board (IRB)-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, patients will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window, unless otherwise specified.

The following assessments and procedures should be performed within 28 days prior to the first dose of study treatment:

- Informed consent
- Review of eligibility criteria
- Medical history and demographics
- Review of prior/concomitant medications
- Physical exam
- ECOG performance status
- Vitals signs (blood pressure, respiratory rate, pulse, oral or temporal temperature), weight, and height
- 12-lead electrocardiogram (ECG)
- MUGA scan or ECHO. The same method must be used throughout the duration of the study.
- Clinical laboratory tests for: ○ Hematology (Table 5) ○ Clinical chemistry (Table 6)
  - Serum (β-hCG) pregnancy test (for women of childbearing potential only)
  - Hepatitis B and C and HIV
- AEs must be captured from the time of consent

Findings from medical history (obtained at screening) and physical exam shall be given a baseline grade according to the procedure for AEs. Increases in severity of preexisting conditions during the study will be considered AEs, with resolution occurring when the grade returns to the ≤ Grade 1 or baseline.

Table 5: Hematology Laboratory Tests

Basophils	MCV
Eosinophils	Hematocrit
Monocytes	Hemoglobin
Neutrophils	Platelet count
Lymphocytes	RBC count
MCH	Total WBC count
MCHC	ANC

ANC = absolute neutrophil count; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; WBC = white blood cell.

Table 6: Clinical Chemistry Laboratory Tests

Albumin	Glucose
ALP	LDH
ALT	Uric acid
AST	Potassium
BUN	Sodium
Chloride	TB
Creatinine	Carbon dioxide
Total protein	Calcium
Amylase	

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; LDH = lactate dehydrogenase; TB = total bilirubin.

8.1.2 Baseline phase

The following assessments and procedures should be performed within 7 days prior to the first dose of study treatment:

- Physical exam including vital sign (blood pressure, respiratory rate, pulse, oral or temporal temperature) and weight measurements
- ECOG performance status
- Thyroid-stimulating hormone (TSH) Clinical laboratory tests for:
  - Hematology (Table 5) o Clinical chemistry (Table 6)
  - Activated partial thromboplastin time and international normalized ratio will be performed at baseline and when clinically
  - Urinalysis by dipstick will be performed at baseline and when clinically indicated (Table 7)
- Mammogram, breast ultrasound, and breast magnetic resonance imaging (MRI). Mammogram and breast ultrasound performed as standard of care can be used for baseline if performed within 90 days prior to the Cycle 1, Day 1 dose of trastuzumab, pertuzumab, and durvalumab. Breast MRI performed as standard of care can be used for baseline if performed within 60 days prior to the Cycle 1, Day 1 dose of trastuzumab, pertuzumab, and durvalumab.
- Core biopsy and collection of tumor tissue
- Research blood collection for circulating DNA

Only screening procedures not performed within 7 days prior to the first dose of study treatment are required at baseline.

Table 7: Urinalysis Tests[a]

Bilirubin	pH
Blood	Protein

Glucose	Specific gravity
Ketones	Color and appearance

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

8.1.3 Treatment phase

Assessments will be performed at the time points specified in the Schedule of Assessments. A window of ± 5 days is allowed for study visits and assessments (except as otherwise specified). EOT is defined as 7 to 10 days after the last dose of study treatment. Note: All assessments on infusion days are to be performed prior to infusion. Results of hematology and clinical chemistry results must be available before commencing an infusion.

8.1.3.1 Adverse event monitoring

The investigator or qualified designee will assess each patient to evaluate for potential new or worsening AEs from the time of ICF signing through 30 days after the last dose of study treatment. AEs will be graded and recorded throughout the study and during the follow-up period according to the NCI CTCAE v5. Toxicities will be characterized in terms of seriousness, causality, toxicity grading, and action taken with regard to the study treatment.

Refer to Section 9 for detailed information regarding the assessment and recording of AEs.

8.1.3.2 Physical exam

Physical exam including vital sign (blood pressure, respiratory rate, pulse, oral or temporal temperature) and weight measurements will be performed before every cycle and at EOT.

8.1.3.3 ECOG performance status

ECOG performance status assessment will be performed before every cycle and at EOT.

8.1.3.4 12-Lead ECG and MUGA scan or ECHO

Twelve-lead ECG will be performed after Cycle 2, at EOT, and when clinically indicated.

Resting 12-lead ECGs will be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

In case of clinically significant ECG abnormalities, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 9.3.5.

MUGA scan or ECHO will be performed after Cycle 2, at EOT, and when clinically indicated. The same method must be used throughout the duration of the study.

8.1.3.5 Tumor imaging and disease assessment

Mammogram and breast ultrasound will be repeated after Cycle 3 (+/- 3 days) and EOT, as per standard of care.
Breast MRI will be performed at EOT.

8.1.3.5.1 Response Evaluation Criteria in Solid Tumors 1.1

The Response Evaluation Criteria in Solid Tumors 1.1 will be used to assess treatment response. All measurable lesions (up to 5 measurable lesions [2/organ]) representative of all involved organs should be identified as target lesions and recorded and measured at baseline. A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter.

- Complete Response (CR)

Disappearance of all target lesions.

- Partial Response (PR)

At least a 30% decrease in the sum of the longest diameter of target lesions, using the baseline sum longest diameter as a reference.

- Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), using the smallest sum longest diameter recorded since treatment start as a reference.

- PD

At least a ≥20% increase in the sum of the longest dimensions of the target lesions taking as a reference the smallest sum longest diameter recorded since treat start, or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

- Clinical PD

Patients who in the opinion of the treating principal investigator have clinical evidence of PD may be classified as having PD.

8.1.3.6 Laboratory procedures/assessments

8.1.3.6.1 Hematology and clinical chemistry

Hematology and clinical chemistry will be performed before every cycle, at EOT, and when clinically indicated. Hematology and clinical chemistry assessments to be performed are listed in Tables 5 and 6 (Section 8.1.1 − Screening phase).

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded in the CRF. Situations in which laboratory safety results should be reported as AEs are described in Section 9.3.5.

If a patient shows an AST or ALT ≥3 × ULN together with TB ≥2 × ULN, refer to Appendix 1 for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

8.1.3.6.2 Thyroid-stimulating hormone

TSH will be measured before every cycle, at EOT, and when clinically indicated. If TSH is measured within 14 days prior to Cycle 1, Day 1, it does not need to be repeated at Cycle 1, Day 1.

Free triiodothyronine or free thyroxine will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

8.1.3.7 Correlative studies

Correlative studies will include tissue and blood-based evaluation of molecular and genetic biomarkers of response and resistance to durvalumab with trastuzumab and pertuzumab combination.

8.1.3.7.1 Tumor tissue collection

All patients will have biopsy at EOT. Tissue will also be collected at the time of surgery. Collected biopsy and surgical tissues will be used for determination of pathological response and correlative studies. RNA will be extracted from de-identified tissue blocks collected during the trial and provided to IDIBAPS Hospital Clinic Barcelona for additional correlative studies at the following address:

IDIBAPS Hospital Clinic Barcelona
Casanova 143
08036 Barcelona

8.1.3.7.2 Blood collection for plasma circulating DNA analysis

Blood sample collection for plasma circulating DNA analysis will be performed after Cycle 2 and at EOT.

8.1.4 Other procedures

8.1.4.1 Safety follow-up

The safety follow-up visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anticancer therapy, whichever comes first. All AEs that occur prior to the safety follow-up visit should be recorded. Patients with an AE of > Grade 1 will be followed until the resolution of the AE to ≤ Grade 1 or baseline. SAEs that occur within 30 days of EOT should also be followed and recorded.

8.1.4.2 Disease-free survival follow-up

Mammogram and breast ultrasound will be performed post-surgery (± 7 days) per standard of care until second primary cancer, relapse, death, or withdrawal of consent. Computed tomography will be performed when clinically indicated.

9 ASSESSMENT OF SAFETY

The principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

9.1 Safety parameters

9.1.1 Definition of adverse events

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

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

AEs may be treatment emergent (i.e., occurring after initial receipt of investigational product) or non-treatment emergent. A non−treatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the patient has received investigational product.

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

The term AE is used to include both serious and non-serious AEs.

9.1.2 Definition of serious adverse events

A SAE is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfills one or more of the following criteria:

- Results in death
- Is immediately life threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect in offspring of the patient
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above
    - Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

9.1.3 Definition of adverse events of special interest (AESIs)

An AE of special interest (AESI) is one of scientific and medical interest specific to the understanding of durvalumab and may require close monitoring. An AESI may be serious or nonserious.

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

AESIs observed with durvalumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- Hepatitis / Transaminase increases
- Endocrinopathies (i.e., events of hypophysitis/hypopituitarism, adrenal insufficiency, hyperthyroidism 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, myasthenia gravis)
  □ Intestinal Perforation
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological, 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 IB. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines in Appendix 1. These guidelines apply to AEs considered causally related to durvalumab by the reporting investigator.

9.2 Assessment of safety parameters

9.2.1 Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v5.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 9.1.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several

hours may not meet the regulatory definition of an SAE and would be considered a non-serious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

9.2.2 Assessment of relationship

A guide to the interpretation of the causality question is found in the Dosing Modification and Toxicity Management Guidelines in Appendix 1.

9.3 Recording of adverse events and serious adverse events

AEs and SAEs will be collected from the time of the patient signing the ICF until the follow-up period is completed (30 days after the last dose of study treatment). If an event that starts post the defined safety follow-up period noted above is considered to be due to a late onset toxicity to study treatment then it should be reported as an AE or SAE, as applicable.

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

Any AEs that are unresolved at the patient's last study visit are followed up by the investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

The following variables will be collected for each AE:

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

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

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

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

- Date the AE met criteria for SAE
- Date the investigator became aware of the SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 9.2.2
- Description of the SAE

The grading scales found in the NCI CTCAE v5 will be utilized for all events with an assigned CTCAE grading. A copy of the CTCAE v5 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

9.3.1 Study recording period and follow-up for adverse events and serious adverse events

AEs and SAEs will be recorded from time of signature of informed consent, throughout the treatment period, and the follow-up period (30 days after the last dose of study treatment).

During the course of the study, all AEs and SAEs should be proactively followed up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

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

9.3.2 Causality collection

The investigator will assess causal relationship between the study treatment and each AE and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the study treatment?”

For SAEs, causal relationship will the study treatment and study procedures will also be assessed. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as “yes.”

A guide to the interpretation of the causality question is found in the Dosing Modification and Toxicity Management Guidelines in Appendix 1.

9.3.3 Relationship to protocol procedures

The investigator is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non−treatment-emergent (i.e., SAEs that occur prior to the administration of study treatment) and treatment-emergent SAEs. A protocolrelated SAE may occur as a result of a procedure or intervention required during the study (e.g., blood collection). The following guidelines should be used by the investigator to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the patient’s medical record.

- Not protocol related: The event is related to an etiology other than the procedure or intervention that was described in the protocol. The alternative etiology must be documented in the study patient's medical record.

9.3.4 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

9.3.5 Adverse events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should, therefore, only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of study treatment.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Whenever possible, the reporting investigator should use the clinical rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AEs.

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical exam as compared with the baseline assessment will be reported as an AE.

9.3.6 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq$3 × ULN together with TB $\geq$2 × ULN may need to be reported as SAEs. Please refer to Appendix 1 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

9.3.7 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the study treatment is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as an AE during the study.

9.3.8 New cancers

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

9.3.9 Deaths

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

- Death clearly resulting from disease progression should be reported to the sponsor and AstraZeneca. The event should be documented in the CRF in the Statement of Death page. It should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the sponsor (CTOMgmt@houstonmethodist.org) and AstraZeneca (AEMailboxClinicalTrialTCS@astrazeneca.com) as an SAE within 24 hours. It should also be documented in the Statement of Death page in the CRF. The report should contain a comment regarding the coinvolvement of disease progression, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the CRF. A postmortem may be helpful in the assessment of the cause of death, and if performed, a copy of the postmortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.

Deaths occurring after the protocol-defined safety follow-up period (30 days after the administration of the last dose of study treatment) should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined safety follow

upperiod and the event is considered to be due to a late onset toxicity to study treatment, then it should also be reported as an SAE.

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

Follow-up of unresolved adverse events
Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF. After 30 days, only patients with ongoing study treatment-related SAEs will continue to be followed for safety.

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

Post-study events
After the patient has been permanently withdrawn from the study, there is no obligation for the investigator to actively report information on new AEs or SAEs occurring in former study patients after the 30-day safety follow-up period. However, if an investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to the study treatment, the investigator should notify the study sponsor and AstraZeneca/MedImmune Drug Safety.

9.3.10 Reporting of serious adverse events

All SAEs will be reported, whether or not considered causally related to the study treatment 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 30 days after the last dose of study treatment or until the initiation of alternative anticancer therapy. The investigator or qualified designee are responsible for informing the FDA (via the Houston Methodist Research Institute Office of Regulatory Affairs & Translational Management) and IRB of the SAE as per local requirements.

The investigator or qualified designee must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected AEs that occur in accordance with the reporting obligations of 21 CFR 312.32. This will be done through the Houston Methodist Research Institute Office of Regulatory Affairs & Translational Management. A copy of the MedWatch/AdEERs report must be sent to the Houston Methodist Research Institute Office of Regulatory Affairs & Translational Management (pamendoza@houstonmethodist.org; fax line: 713-793-7001). The investigator or qualified designee will concurrently forward all such reports to the sponsor

(CTOMgmt@houstonmethodist.org) and AstraZeneca. A copy of the MedWatch/AdEERs report must be emailed to AstraZeneca (AEMailboxClinicalTrialTCS@astrazeneca.com) at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to the sponsor and AstraZeneca at the same time.

* A ***cover page*** should accompany the ***MedWatch/AdEERs*** form indicating the following:
- "Notification from an Investigator-Sponsored Study"
- The investigator's name and address
- The study name/title and AstraZeneca ISS reference number (ESR-18-13489)

* The investigator must also indicate, either in the SAE report or the cover page, the ***causality*** of events ***in relation to all study medications*** and if the SAE is ***related to disease progression***.

* ***Send the SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox:*** AEMailboxClinicalTrialTCS@astrazeneca.com

The SAE report should also be sent to the Houston Methodist Research Institute Office of Regulatory Affairs & Translational Management at: RATM@houstonmethodist.org fax line: 713-793-7001

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to the sponsor (CTOMgmt@houstonmethodist.org), AstraZeneca, the FDA (via the Houston Methodist Research Institute Office of Regulatory Affairs & Translational Management), and the IRB.

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

9.3.11 Reporting of deaths to AstraZeneca

All deaths that occur during the study, or within the protocol-defined 30-day post-last dose of study treatment safety follow-up period must be reported to AstraZeneca as follows:

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

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to AstraZeneca as an SAE within **24 hours** (see Section 9.3.10 for further details). The report should contain a comment regarding the coinvolvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

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

Deaths that occur following the protocol-defined safety follow-up period (30 days after the last dose of study treatment) will be documented as events for DFS analysis, but will not be reported as an SAE. However, if an investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to the study treatment, the investigator should notify the sponsor and AstraZeneca/MedImmune Drug Safety.

9.3.12 Other events requiring reporting

9.3.12.1 Overdose

An overdose is defined as a patient receiving a dose of durvalumab in excess of that specified in the IB, unless otherwise specified in this protocol.

Any overdose of durvalumab, with or without associated AEs/SAEs, in a study patient is required to be reported within 24 hours of knowledge of the event to the sponsor (CTOMgmt@houstonmethodist.org) and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety emailbox (AEMailboxClinicalTrialTCS@astrazeneca.com). If the overdose results in an AE, the AE must also be recorded as an AE (Section 9.3). 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 (Section 9.3.10).

There is currently no specific treatment in the event of an overdose of durvalumab. The investigator will use clinical judgment to treat any overdose.

9.3.12.2 Hepatic function abnormality

Hepatic function abnormality in a study patient that fulfills the biochemical criteria of a potential Hy's Law case, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor

(CTOMgmt@houstonmethodist.org) and AstraZeneca Patient Safety using the designated Safety emailbox (AEMailboxClinicalTrialTCS@astrazeneca.com), unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to the study treatment has been confirmed. The criteria for a potential Hy's Law case is AST or ALT ≥3 × ULN together with TB ≥2 × ULN at any point during the study following the start of study treatment irrespective of an increase in ALP.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to the study treatment, the decision to continue dosing of the study patient will be based on the clinical judgment of the investigator.

- If no definitive underlying diagnosis for the abnormality is established, dosing of the study patient must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

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

9.3.12.3 Pregnancy

9.3.12.3.1 Maternal exposure

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

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

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

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

The same timelines apply when outcome information is available.

10 STATISTICAL METHODS

This Phase II study will be conducted using a Simon's minimax two-stage design. A null response rate of 35% is assumed.[16] The target response rate for the regimen will be 52%. When the probability of accepting a "bad" regimen (i.e., response rate ≤35%) is 0.10 (i.e., alpha) and the probability of rejecting a "good" regimen (i.e., response rate ≥52) is 0.20 (i.e., beta or 1 – power), Simon's minimax design requires 15 patients in the first stage. If 4 or fewer patients respond to the regimen, the study will be stopped and the regimen will be declared as ineffective. If at least 5 of the first 15 patients respond, 24 additional patients will be entered on the study to reach a total of 39 patients. At the end of the second stage, the regimen will be rejected if the response rate is less than or equal to 17 out of 39 patients and will be accepted otherwise. This design yields a type I error rate of $\alpha = 0.096$ (targeted rate of 0.10) and power of 80.1% (targeted power of 80%) when the true response rate is 0.52. When the true response rate is 35% (i.e., null hypothesis is true), the probability of stopping the study early (i.e., after the first stage) is 35.2%. On the other hand, if the true response rate is 52%, the probability of stopping the study early is only 4.3%. The expected sample size is 30.6 if the response rate is 35% and 38.0 if the true response rate is 52%. If there are 4 or fewer responders in the first 15 patients, the probability of achieving a significant result at the end of stage 2 is only 0.0002 (the futility rate), assuming the observed data in stage 1 provides a reasonable estimate of the response rate.

As a measure of safety, an initial cohort of 3 patients will be followed for toxicity through the first cycle of trastuzumab, pertuzumab, and durvalumab. If no more than 1 of 3 patients experience toxicity (i.e., if 2 of the first 3 patients experience toxicity, the study will stop immediately), then 3 more patients will be enrolled. If no more than 1 of 6 patients experience toxicity (again, the study would stop if 2 of the first 6 patients experience toxicity), then the study will be fully opened. Toxicity will be defined as any treatment-related death or any ≥ Grade 3 AE excluding alopecia and constitutional symptoms (as assessed by the NCI CTCAE v5). Additionally, toxicity after the first 6 patients will be monitored based on a beta-binomial model, assuming *a priori* that the probability of toxicity p is distributed beta(1, 1). Study accrual will be suspended and the safety profile of the combination will be reviewed by the safety monitoring committee if $P_r(p > .30 \mid \text{data}) > 0.95$. This stopping rule yields the following stopping bounds where the numerator represents the number of events needed to suspend accrual and the denominator represents the number treated at that point in the study: 7/12, 8/14, 9/17, 10/20, 11/22, 12/25, 13/28, 14/30, 15/33, and 16/36. Scenario 1 of the operating characteristics table (Table 8) indicates that the probability of stopping the study early for toxicity is low when the combination is safe; that is, the study has an 11% chance of stopping early when the true toxicity

rate is 10%. The study has an 89.9% chance of stopping for toxicity if the true toxicity rate is 45% and on average would take only 4 patients to arrive at that conclusion.

Table 8: Operating Characteristics for Toxicity Monitoring Rule

Scenario	True P_r(toxicity)	P_r(stop early)	Median No. of Patients (25%, 75%)
1	0.10	00.1116	39 (39, 39)
2	0.20	00.3366	39 (5, 39)
3	0.30	00.5954	6 (4, 39)
4	0.45	00.8988	4 (3, 6)
5	0.60	00.9952	3 (2, 4)

At the end of the study, the response rate and its associated 95% Wilson score CI will be reported. With 39 patients, the response rate CI will be no wider than 29.9 percentage points. The overall toxicity rate and CI will be reported, and the toxicity profile of the regimen will be summarized. This trial was designed using PASS 13.0.8 and the Multc99 software developed by the Biostatistics Department of the University of Texas MD Anderson Cancer Center.

11 ETHICAL AND REGULATORY REQUIREMENTS

11.1 Ethical conduct of the study

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki. The study will comply with U.S. FDA regulations and applicable local, state, and federal laws.

11.2 Ethics and regulatory review

The protocol and ICF will be submitted to the FDA and IRB for review and approval. Approval of both the protocol and ICF must be obtained before any patient is enrolled in the study. Any amendment to the protocol and ICF will require review and approval by the FDA and IRB before implementation. The patient or her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the patient's dated signature or by the patient's legally acceptable representative's dated signature.

11.3 Patient confidentiality

The sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF signed by the patient, unless permitted or required by law. Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities and the IRB.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances; however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to her genetic data. Also, regulatory authorities may require access to the relevant files, although the patient's medical information and the genetic files would remain physically separate.

11.4 Informed consent

The investigator or qualified designee will obtain documented consent from each potential patient prior to participating in the study. The ICF will be FDA and IRB approved and the patient will be asked to read and review the document. The investigator will explain the research study to the patient and answer any questions that may arise. All patients will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Patients will have the opportunity to carefully review the written ICF and ask questions prior to signing. Patients should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Consent must be documented by the patient's dated signature or by the patient's legally acceptable representative's (LAR) dated signature on the ICF along with the dated signature of the person conducting the consent discussion. Patients may withdraw consent at any time throughout the course of the study. A copy of the signed and dated ICF will be given to the patients for their records. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. In the event that time and distance are of concern and it will prevent the potential patient and/or their LAR from being present to sign the consent form in person, Informed consent can be orally obtained by a delegated member of the research team by telephone, or through a Houston Methodist-vetted system enabling a virtual 'face to face' discussion, provided that one additional person monitors the process and there is written documentation in the research record including confirmation of the person consenting,

their name and their relationship to the patient; the date and time consent was given; the protocol for which the consent was given.

A copy of the Full IRB approved consent must be transmitted to the potential subject or LAR prior to initiating the consent process. If relying on telephone consent, the participant or LAR must sign the consent and can either mail or scan and send the consent electronically to the research team. The research team will sign and return a final, signed copy to the participant or LAR. Research procedures cannot begin before the informed consent is fully documented.11.5 Changes to the protocol and informed consent form

Any change or addition to this protocol that significantly affects patient safety, the scope of the investigation, or the scientific quality of the study requires approval by the FDA and IRB. Examples of amendments requiring such approval are:

- increases in drug dose or duration of patient exposure
- significant changes in the study design (e.g., addition or deletion of a control group)
- increase in the number of invasive procedures
- addition or deletions of a test procedure required for safety monitoring

These requirements for approval should 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 study. The FDA and IRB must be informed of any immediate protocol changes implemented by the investigator for safety reasons. Amendments affecting administrative aspects of the study do not require formal protocol amendments but do require IRB approval.

12 STUDY MANAGEMENT

12.1 Training of study site personnel

Before the first patient is entered into the study, the investigator or qualified designee will review and discuss the requirements of the clinical study protocol with the investigational staff at the primary and participating sites.

Proper handling and shipment of biological samples will be reviewed and discussed with investigators and investigational staff at the other participating centers.

12.2 Monitoring of the study

An independent research monitor will conduct periodic monitoring visits during study conduct to ensure GCP are being followed, to confirm the investigational team is adhering to the protocol, and to confirm data are being accurately and timely recorded in the CRFs. The investigator and

sponsor will allow the monitor direct access to source documents to perform this verification. The monitor will report his/her observations/findings to the IRB.

13 DATA MANAGEMENT

CRFs will be designed and utilized to capture all patient data. An electronic database will be designed to store patient CRFs. The investigational staff will ensure that data are recorded in the CRF as specified in the study protocol. Data quality control will be performed regularly by the investigational staff to ensure timely, accurate, and complete patient data collection as well as protocol compliance. Queries will be generated and resolved prior to the generation of interim and final summary reports.

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Appendix 1

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy – August 2024

General Considerations Regarding Immune-Mediated Reactions

These guidelines are provided as a recommendation to support investigators in the management of potential immunemediated adverse events (imAEs).

Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO)) in the management of these events. Refer to the section of the table titled "Other -Immune-Mediated Reactions" for general guidance on imAEs not noted in the "Specific Immune-Mediated Reactions" section. Early identification and management of imAEs is essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying imAEs. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold study drug/study regimen for severe (Grade 3) imAEs. Permanently discontinue study drug/study regimen for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids. Based on the severity of the imAE, durvalumab and/or tremelimumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines. With long-term steroid and other immunosuppressive use, consider the need for glucose monitoring.
Dose modifications of study drug/study regimen should be based on severity of treatment-emergent toxicities graded per NCI CTCAE version in the applicable study protocol.

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

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

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; ESMO European Society for Medical Oncology

Relevant Society Guidelines for Management of imAEs

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

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Cancer 2021, version 1.2;9:e002435
2. Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of
Clinical Oncology (ASCO) Guideline Update. J Clin Oncol 2022;39(36):4073-4126.
3. Haanen J, et al. Management of toxicities from immunotherapy: European Society for Medical Oncology (ESMO) clinical practice guideline for diagnosis,
treatment, and follow-up. Annals Oncol 2022;33(12):1217-1238.
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7, 2022.

Pediatric Considerations Regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTCAE grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks of** initiating corticosteroids.	– All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for steroid dosing (i.e., mg/kg/day) provided for adult patients should also be used for pediatric patients. – The recommendations for IVIG and plasmapheresis use provided for adult patients may be considered for pediatric patients. – The infliximab 5 mg/kg IV one time dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For subsequent dosing and dosing in children < 6 years old, consult a pediatric specialist. – For pediatric dosing of mycophenolate mofetil, consult a pediatric specialist.

- With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** - Patients should be thoroughly evaluated to rule out any alternative etiology with similar clinical presentation (e.g infection,progressive disease). - Monitor patients for signs (e.g. tachypnoea) and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Evaluate patients with imaging and pulmonary function tests, including other diagnostic procedures as described below. - Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related etiologies excluded, and managed as described below. - Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up (including clinically relevant culture specimens to rule out infection), and high- resolution CT scan. - Consider Pulmonary and Infectious Diseases consults.
	Grade 1	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up, and then as clinically indicated.

	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper (<10 mg prednisone or equivalent).	**For Grade 2** - Monitor symptoms daily and consider hospitalization as clinically indicated. - Consider Pulmonary and Infectious Diseases Consults; - Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). - Consider HRCT or chest CT with contrast.Repeat imaging study as clinically indicated. - If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. - If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy. such as tumor necrosis factor (TNF) inhibitors (e.g., infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. - Consider, as necessary, discussing with clinical study lead.
	Grade 3 or 4	Permanently discontinue study drug/study regimen	**For Grade 3 or 4** - Hospitalize the patient - Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent - Obtain Pulmonary and Infectious Diseases Consults; consider discussing with Clinical Study Lead, as needed - Supportive care (e.g. oxygen) - If no improvement within 2 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade**	**General Guidance**	- For Any Grade - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease

	(Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)		progression, other medications, or infections), including testing for *Clostridium difficile* toxin, etc. - Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). - Consider further evaluation with imaging study with contrast. - Consult a gastrointestinal (GI) specialist for consideration of further workup. - **WHEN SYMPTOMS OR EVALUATION INDICATE AN INTESTINAL PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY.** - **PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION**. - Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade events, including intestinal perforation. - Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1	No dose modifications	**For Grade 1** - Monitor closely for worsening symptoms. - Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide, and other supportive care measures. - If symptoms persist, consider checking lactoferrin and/or calprotectin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 - If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper (<10 mg	**For Grade 2** - Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. - Consider further evaluation with imaging study with contrast. - Consider consult of a gastrointestinal (GI) specialist for consideration of further workup. - Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.

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

		<u>tremelimumab for Grade 3 diarrhea/colitis. HOLD durvalumab until resolution to Grade ≤ 1; durvalumab alone can be resumed after completion of steroid taper (<10 mg prednisone per day or equivalent)</u> **B. Permanently discontinue both durvalumab and tremelimumab for 1) Grade 4 diarrhea/colitis or 2) Any grade of intestinal perforation** **Grade 4** Permanently discontinue study drug/study regimen.	
Hepatitis ***Infliximab should not be used for management of immune-related hepatitis***	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. viral hepatitis, disease progression, concomitant medications) - Monitor and evaluate transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP]) and total bilirubin.
	ALT or AST < 3x ULN or total bilirubin <1.5. x ULN	- No dose modification - If it worsens, then consider holding therapy.	- Continue transaminase and total bilirubin monitoring per protocol.
	ALT or AST > ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN	Hold study drug/study regimen dose until ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN. Resume study drug/study regimen after completion of steroid taper (<10 mg prednisone or equivalent).	Regular and frequent checking of transaminases and total bilirubin (e.g., every 1 to 2 days) until transaminases and total bilirubin elevations improve or resolve. - Consider checking creatinine phosphokinase (CPK) and aldolase (to rule out myositis) - If no resolution to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN in 1 to 2 days, consider discussing with Clinical Study Lead, as needed.

PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in hepatocellular carcinoma (HCC) or secondary tumor involvement of the liver with abnormal baseline values [BLV])

		- − Permanently discontinue study drug/study regimen for any case meeting Hy's law laboratory criteria (AST or ALT >3 × ULN AND bilirubin ≥2 × ULN without initial findings of cholestasis (i.e., elevated ALP) and in the absence of any alternative cause.	- If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	ALT or AST > 5 <10 x ULN	- Hold study drug/study regimen. - Resume study drug/study regimen if elevations downgrade to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN after completion of steroid taper (<10 mg prednisone, or equivalent). - **If in combination with tremelimumab, do not restart tremelimumab.**	- Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. - Check CPK and aldolase (to rule out myositis) - Perform Hepatology Consult, abdominal workup, and imaging as appropriate. - If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil - 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. Infliximab should NOT be used.
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN ALT or AST > 10 x ULN OR total bilirubin > 3 x ULN	Permanently discontinue study drug/study regimen.	– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.**

			- − Perform Hepatology Consult, abdominal workup, and imaging as appropriate.
Hepatitis **(elevated transaminases and total bilirubin)** *Infliximab should not be used for management of immune-related hepatitis* THIS shaded area is guidance only for management of "Hepatitis (elevated LFTs)" in HCC patients (or secondary tumour involvement of the liver with abnormal baseline values [BLV])	**Any Elevations of AST, ALT, or T. Bili as Described Below**	**General Guidance**	**For Any Elevations Described** - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis**]).** - Monitor and evaluate AST, ALT, ALP, and T. Bili. - For hepatitis B (HBV) + patients: evaluate quantitative HBV viral load, quantitative Hepatitis B surface antigen (HBsAg), or Hepatitis B envelope antigen (HBsAg). - − For hepatitis C (HCV) + patients: evaluate quantitative HCV viral load. - Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HBV medications if HBV viral load is >2000 IU/ml. - Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HCV medications if HCV viral load has increased by ≥2-fold. - For HCV+ with Hepatitis B core antibody (HBcAb)+: Evaluate for both HBV and HCV as above.
See instructions at bottom of shaded area if transaminase rise not isolated but (at any time) occurs in setting of either increasing bilirubin or signs of DILI/Liver decompensation.	Isolated AST or ALT > ULN and ≤ 2.5 x BLV	- No dose modifications. - If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. - For all transaminase elevations , see instructions at bottom of shaded area if transaminase rise if not isolated but (at any time) occurs in setting of **either increasing bilirubin or signs of DILI/Liver decompensation**	

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

			Clinical Lead if mycophenolate is not available. **Infliximab should NOT be used**.
	ALT or AST > 7 x BLV OR > 20 ULN whichever occurs first OR bilirubin > 3 ULN	Permanently discontinue study drug/study regimen	Same as above (except recommend obtaining liver biopsy early)

Nephritis and/or renal dysfunction	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). – Consider consulting a nephrologist. – Consider imaging studies to rule out any alternative etiology. – Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decreased urine output, or proteinuria). – Follow urine protein/creatinine ratio every 3-7 days.
	Grade 1	- No dose modifications	**For Grade 1** – Monitor serum creatinine weekly and any accompanying symptoms. – If creatinine returns to baseline, resume its regular monitoring per study protocol. – If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider hydration, electrolyte replacement, and diuretics, as clinically indicated. – Consider nephrologist consult if not resolved within 14 days, or earlier as clinically indicated.
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. - If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen	**For Grade 2** - Consider including hydration, electrolyte replacement, and diuretics as clinically indicated. . - Follow urine protein/creatinine ratio every 3-7 days - Carefully monitor serum creatinine as clinically warranted.

		after completion of steroid taper (<10 mg prednisone, or equivalent).	- Consult nephrologist and consider renal biopsy if clinically indicated. - Start prednisone 1 to 2 mg/kg/day if other causes are ruled out - If event is persistent beyond 5 days or worsens, increase to prednisone up to 2 mg/kg/day PO or IV equivalent. - If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup. When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** - Carefully monitor serum creatinine daily - Follow urine protein/creatinine ratio every 3-7 days - Consult nephrologist and consider renal biopsy if clinically indicated - Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent - If event is not responsive within 3 to 5 days of steroids or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant.

Dermatologic Adverse Events (Including Pemphigoid)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade** - Patients should be thoroughly evaluated to rule out any alternative etiology. - Monitor for signs and symptoms of dermatitis (rash and pruritus). HOLD STUDY DRUG IF GRADE 3 PEMPHIGOID OR SEVERE CUTANEOUS ADVERSE REACTION (SCAR) IS SUSPECTED. - PERMANENTLY DISCONTINUE STUDY DRUG IF SCAR, OR GRADE 3 PEMPIGOID IS CONFIRMED.
	Grade 1	No dose modifications.	**For Grade 1** - Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or

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

			- Consider, as necessary, discussing with Clinical Study Lead.

Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** Depending on type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). - Consider consulting an endocrinologist for endocrine events. - Consider discussing with Clinical Study Lead, as needed. - Monitor patients for signs and symptoms of endocrinopathies. (Nonspecific symptoms include headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness.) - Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: thyroid stimulating hormone (TSH), free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, hemoglobin A1c (HgA1c)).If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing. - Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
	Grade 1	No dose modifications.	**For Grade 1** - Monitor patient with appropriate endocrine function tests. - For suspected hypophysitis/hypopituitarism, consider consulting an endocrinologist to guide assessment of early-morning adrenocorticotropin hormone (ACTH), cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not

			be useful in diagnosing early secondary adrenal insufficiency). - If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2, 3, or 4	- For Grade 2-4 endocrinopathies <u>other than hypothyroidism and type 1</u> diabetes mellitus (T1DM), consider holding study drug/study regimen dose until acute symptoms resolve. - − Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper (<10 mg prednisone, or equivalent). − Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement.	**For Grade 2-4** - Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. - For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or T1DM, and as guided by an endocrinologist, consider short- term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement. **- Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids.** **- Isolated T1DM may be treated with appropriate diabetic therapy, and without corticosteroids. <u>Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is</u> positive for diabetic ketoacidosis.** - For patients with normal endocrine workup (laboratory assessment or magnetic resonance imaging (MRI) scans), repeat laboratory assessments/MRI as clinically indicated.

Amylase/Lipase increased	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the	**General Guidance**	**For Any Grade** - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression, viral infection, concomitant medications, substance abuse).

	CTCAE grade/severity)		- For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. - Assess for signs/symptoms of pancreatitis - Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT) - If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase - If evidence of pancreatitis, manage according to pancreatitis recommendations
	Grade 1	No dose modifications.	
	Grade 2, 3, or 4	**For Grade 2,3, or -4** In consultation with relevant gastroenterology specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	

Acute Pancreatitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** - Patients should be thoroughly evaluated to rule out any alternative etiology. - Consider Gastroenterology referral.
	Grade 2	Consider holding study drug/regimen	**Grade 2** - Consider IV hydration. - Consider Gastroenterology referral
	Grade 3, or 4	**For Grade 3** Hold study drug/study regimen until resolution of elevated enzymes and no radiologic findings If no elevation in enzymes or return to Baseline values, then resume study drug/study regimen after. completion of steroid taper (<10 mg prednisone, or equivalent). **For Grade 4**	**For Grade 3, or 4** - Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. - IV hydration

		Permanently discontinue study drug/study regimen.	

Nervous System Disorders			
Aseptic Meningitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** - Symptoms may include headache, photophobia, and neck stiffness, nausea/ vomiting which may resemble an infectious meningitis. - Patients may be febrile. - Mental status should be normal	**For Any Grade** - Consider neurology consult - Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. - Exclude bacterial and viral infections. (ie HSV) - Consider antibiotic for bacterial coverage until cultures/panel results are back - Consider IV acyclovir until polymerase chain reactions are available
	Any Grade	Permanently discontinue study drug/study regimen	**For Any Grade** - Consider neurology consult - Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. - Exclude bacterial and viral infections. (ie HSV) - Consider IV acyclovir until polymerase chain reactions are available - Consider, as necessary, discussing with Clinical Study Lead.(Last bullet) - Consider hospitalization. - Once infection has been ruled out promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.
Encephalitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** − Symptoms may include Confusion, altered behaviour, headaches, seizures, short-term memory loss, depressed level of consciousness focal weakness, and speech abnormality.	**For Any Grade** - Consider neurology consult - Consider testing including MRI of the brain with and without contrast, lumbar puncture, electroencephalogram (EEG) to evaluate for subclinical seizures, ESR, CRP, antineutrophil cytoplasmic antibody (ANCA) (if vasculitic process suspected), thyroid panel including TPO and thyroglobulin and additional autoantibodies to rule out paraneoplastic disorders. - Exclude bacterial and viral infections. (i.e. HSV) Consider IV acyclovir until polymerase chain reactions are available. - Add bacterial coverage

	Grade 2	**For Grade 2** Permanently discontinue study drug/study regimen	**For Grade 2** - Consider, as necessary, discussing with the Clinical Study Lead. - Once infection has been ruled out methylprednisolone 1–2 mg/kg/day - For progressive symptoms or if oligoclonal bands are present consider methylprednisolone 1 g IV daily for 3–5 days plus IVIG or plasmapheresis
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen	**For Grade 3 or 4** - Consider, as necessary, discussing with Clinical Study Lead. - Consider hospitalization. - Once infection is ruled out, start methylprednisolone 1 g IV daily for 3–5 days for progressive symptoms consider adding IVIG or plasmapheresis
Demyelinating Disease (optic neuritis, transverse myelitis, acute demyelinating encephalomyelitis (ADEM))	**Any Grade**	**General Guidance** - Permanently discontinue immunotherapy - Consider MRI of the spine and brain Once imaging is complete, consider lumbar puncture. - Consider testing to rule out additional aetiologies: B12, copper, HIV, rapid plasma reagin (RPR), ANA, anti- Ro/La antibodies, aquaporin-4 IgG, myelin oligodendrocyte glycoprotein (MOG) IgG, paraneoplastic panel	**For Any Grade** - Consider neurology consult - Inpatient care - Consider prompt initiation of high methylprednisolone pulse dosing - Strongly consider IVIG or plasmapheresis
Peripheral neuropathy	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** - Patients should be evaluated to rule out any alternative etiology for neuropathy (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the

			neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. - Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation.
	Grade 1	No dose modification	**For Grade 1** - Consider discussing with the Clinical Study Lead, as needed. - Monitor symptoms for interference with ADLS, gait difficulties, imbalance, or autonomic dysfunction
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1**.**	**For Grade 2** - Consult a neurologist. - Consider EMG/NCS - Consider discussing with the Clinical Study Lead, as needed. - Observation for additional symptoms or consider initiating prednisone 0.5–1 mg/kg orally - If progression, initiate methylprednisolone 2–4 mg/kg/day and treat as GBS - Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** - Consider discussing with Clinical Study Lead, as needed. - Recommend hospitalization. - Monitor symptoms and consult a neurologist. - **Treat per Guillain-Barré Syndrome recommendations**
Guillain-Barré Syndrome (GBS)		**General Guidance**	- Recommend hospitalization - Obtain neurology consult - Obtain MRI of spine to rule out compression lesion - Obtain lumbar puncture - Antibody tests for GBS variants - Pulmonary function tests - Obtain electromyography (EMG) and nerve conduction studies - Frequently monitor pulmonary function tests and neurologic evaluations - Monitor for concurrent autonomic dysfunction

			- Initiate medication as needed for neuropathic pain
	Grade 2-4	**Grade 2-4** Permanently discontinue	**Start IVIG or plasmapheresis in addition to methylprednisolone 1 gram daily for 5 days, then taper over 4 weeks.**
Myasthenia gravis		**General Guidance**	- Obtain neurology consult - Recommend hospitalization - Obtain pulmonary function tests - Obtain labs: ESR, CRP, creatine phosphokinase (CPK), aldolase and anti-striational antibodies - Consider cardiac exam, ECG, troponin, transthoracic echocardiogram for possible concomitant myocarditis - Obtain electromyography (EMG) and nerve conduction studies - Consider MRI of brain/spine to rule out CNS involvement by disease - Avoid medications that might exacerbate MG (e.g.beta blockers, some antibiotics, IV magnesium
	Grade 2	Permanently discontinue	- Consider pyridostigmine 30mg three times daily and gradually increase based on symptoms (max dose 120mg four times daily) - Consider starting low dose prednisone 20mg daily and increase every 3-5 days. (Target dose 1mg/kg/day. Max dose 100mg daily)
	Grade 3-4	Permanently discontinue	- Start methylprednisolone 1-2mg/kg/day. Taper steroids based on symptom improvement - Start plasmapheresis or IVIG - Consider rituximab if refractory to plasmapheresis or IVIG - Frequent PFT assessments - Daily neurologic evaluations
Myocarditis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** Discontinue drug permanently if biopsy proven immune-mediated myocarditis.	**For Any Grade** - Initial work-up should include clinical evaluation, B type natriuretic peptide (BNP), cardiac enzymes, electrocardiogram (ECG), echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)

			- The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. - Consider discussing with the Clinical Study Lead, as needed. - Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early, to promptly assess whether and when to complete a cardiac biopsy, including any other diagnostic procedures. - as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed.
	Grade 2, 3 or 4	If Grade 2-4 permanently discontinue study drug/study regimen	**For Grade 2-4** - Monitor symptoms daily, hospitalize. - Consider cardiology consultation and prompt start of high-dose/pulse corticosteroid therapy - Supportive care (e.g., oxygen). - If no improvement consider additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab), IVIG or plasmapheresis or other therapies depending on the clinical condition of the patient, based on the discretion of the treating specialist consultant r or relevant practice guidelines. **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.**
Myositis/ Polymyositis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General Guidance	**For Any Grade** - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections). - Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, and; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and

			fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. - If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. - Consider, as necessary, discussing with the Clinical Study Lead. - **Consider that patients may present with or progress to rhabdomyolysis. Treat signs and symptoms as per institutional protocol or local clinical practice.** - Initial work-up should include clinical evaluation, creatine kinase, aldolase, lactate dehydrogenase (LDH), blood urea nitrogen (BUN)/creatinine, erythrocyte sedimentation rate or C-reactive protein (CRP) level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia.
	Grade 1	No dose modification	**For Grade 1** - Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. - Consider Neurology consult - Consider, as necessary, discussing with the Clinical Study Lead.
	Grade 2	- Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study	**For Grade 2** - Monitor symptoms daily and consider hospitalization.

		drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	- Consider Rheumatology or Neurology consult, and initiate evaluation. - Consider, as necessary, discussing with the Clinical Study Lead. - If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant - If clinical course is not rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day - If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 days, consider additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab), IVIG or plasmapheresis, or other therapies based on the discretion of the treating specialist consultant or relevant practice guideline **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**
	Grade 3	For Grade 3 - Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 3** - Monitor symptoms closely; recommend hospitalization. - Consider Rheumatology and/or Neurology consult - Consider discussing with the Clinical Study Lead, as needed. - Promptly start IV methylprednisolone 2 to4 mg/kg/day systemic steroids along with receiving input from Neurology consultant If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.** - Consider whether patient may require IV IG, plasmapheresis.

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

Other – Immune-mediated Reactions

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

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

Infusion-Related Reactions

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

Non-Immune-Mediated Reactions

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

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

APPENDIX 2

ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
Oken MM, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.	