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DuRvalumab (MEDI4736) with chEmotherapy as first line treAtment in advanced pleural Mesothelioma - A phase 3 Randomised trial

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DREAM3R

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Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANZ	Australia and New Zealand
AR DRG	Australian Refined Diagnostic Related Groups
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AZ	AstraZeneca
CI	Confidence interval
CL	Clearance
Cr	Creatinine
CR	Complete response
CRF	Case report form
ctDNA	circulating tumour deoxyribonucleic acid
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
DCO	Data cut-off
DCR	Disease control rate
DOA	Delegation of Authority
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC	European Organisation for the Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5 dimensions 5 levels questionnaire
FFPE	Formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HR	Hazard ratio
HREC	Human research ethics committee
HRQL	Health Related Quality of Life
IB	Investigator Brochure
iBOR	Immune best overall response
ICH	International Conference on Harmonization
ICI	Immune Checkpoint Inhibitor
iCPD	Immune confirmed progressive disease
iCR	Immune complete response
IgG	Immunoglobulin G
ILD	Interstitial lung disease
imAEs	Immune-mediated Adverse Events
IMP	Investigational Medicinal Product
INR	International normalized ratio
IO	Immunotherapy
IP	Intellectual property
iPR	Immune partial response
IRB	Institutional Review Board

iRECIST	Immune RECIST
iSD	Immune stable disease
ISDMC	Independent Safety and Data Monitoring Committee
ITSC	International Trial Steering Committee
ITT	Intention to treat
iUPD	Immune unconfirmed progressive disease
IV	Intravenous(ly)
kg	Kilogram
m^2	metres squared
mAb	Monoclonal antibody
MBS	Medicare Benefits Schedule (Australia only)
mg	Milligram
mL	Milliliter
mM	Millimolar
MOA	Mechanism of action
mRECIST 1.1	Modified RECIST 1.1
mRNA	Messenger ribonucleic acid
NCARD	National Centre for Asbestos Related Diseases
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not Evaluable
NHMRC CTC	National Health and Medical Research Council, Clinical Trials Centre
NL	New lesion
NLT	New lesion target
NLNT	New lesion non target
NR	Not reached
NSCLC	Non-small cell lung cancer
OR	Objective response
ORR	Objective response rate
OS	Overall survival
OTR	Objective tumour response
PBMC	Peripheral blood mononuclear cell
PBS	Pharmaceutical Benefits Scheme (Australia only)
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PFS6	6-month progression-free survival
PK	Pharmacodynamics
PM	Pleural mesothelioma
PR	Partial response
PrECOG	Pr Eastern Cooperative Oncology Group
PRO	Patient reported outcome
PT	Prothrombin time
PTT	Partial thromboplastin time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QALY	Quality adjusted life year
QAS	Quality adjusted survival
QLQ-C30	EORTC Quality of Life Questionnaire Cancer 30 questions
QLQ-LC29	EORTC Quality of Life Questionnaire Lung Cancer 29 questions

QoL	Quality of Life
QTcF	The time between the start of the Q wave and the end of the T wave corrected for heart rate using the formula by Fridericia
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
RR	Response rate
RT	Radiotherapy
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Stable disease
SH2	Src homology 2
SoC	Standard of care
SSI	Significant safety issue
STAT	Signal transducer and activator of transcription
SUSAR	Suspected unexpected serious adverse reaction
TB	Total bilirubin
TGA	Therapeutic Goods Administration
TMC	Trial Management Committee
TOGA	Thoracic Oncology Group of Australasia
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
USA	United States of America
USM	Urgent Safety Measure
USPI	United States Package Insert
vs	Versus
(w/v)	Weight/volume
WOCBP	Women of child bearing potential
WT	Weight
°C	Degrees Celsius
°F	Degrees Fahrenheit

Table of Contents

1 SYNOPSIS AND SCHEMA 10
2 Background 13
2.1 Mesothelioma Epidemiology 13
2.2 Current Treatment Options in Mesothelioma 13
2.3 Durvalumab Background/Non-Clinical and Clinical Experience 13
2.3.1 Overall Risks 14
2.4 AEs of Immune Checkpoint Inhibitors 14
2.5 Rationale for Immune Checkpoint Blockade in Mesothelioma 15
2.6 First Line Dual Immune Checkpoint Blockade 16
2.7 Rationale for Combining Cisplatin/Pemetrexed Chemotherapy with Immune Checkpoint Blockade 16
2.8 Results from the Single Arm 'DREAM' Clinical Trial 17
2.9 Results from the Single Arm "PrE0505" Clinical Trial 19
2.10 Rationale for Fixed Dosing 20
2.11 Rationale for this Trial 20
3 AIM AND OBJECTIVES 21
4 DESIGN 21
5 STUDY POPULATION 21
5.1 Target Population 21
5.2 Inclusion Criteria 22
5.3 Exclusion Criteria 22
5.4 Study Enrolment 24
5.4.1 Screening 24
5.4.2 Randomisation 24
6 TREATMENT PLAN 24
6.1 Treatments 24
6.2 Durvalumab 26
6.2.1 Durvalumab Administration 26
6.2.2 Monitoring of Durvalumab Dose Administration 27
6.2.3 Durvalumab Dose Delay and Management of Treatment Related Adverse Events 27
6.2.4 Criteria to Discontinue Durvalumab Permanently 27
6.3 Cisplatin/Carboplatin and Pemetrexed 28
6.3.1 Cisplatin/Carboplatin and Pemetrexed Dose Administration 28
6.3.2 Cisplatin/Carboplatin and Pemetrexed Dose Modification and Discontinuation Criteria 29
6.3.3 Retreatment Criteria for Cisplatin/Carboplatin and/or Pemetrexed 30
6.3.4 Toxicity Management Guidelines for Chemotherapy and Durvalumab Combination 30
6.4 Ipilimumab and Nivolumab 31
6.4.1 Ipilimumab and Nivolumab Administration 31
6.4.2 Dose Modifications for Ipilimumab and Nivolumab 31
6.4.3 Dose Delays Ipilimumab and Nivolumab 31
6.4.4 Criteria to Resume Ipilimumab and Nivolumab 32
6.4.5 Management of Infusion Related Reactions to Ipilimumab or Nivolumab 32
6.4.6 Permanent Discontinuation of Ipilimumab or Nivolumab 32
6.5 Post-Study Treatment 33
6.6 Concomitant Medications 33
6.6.1 Recommended for Pemetrexed 33
6.6.2 Permitted 34

6.6.3 Prohibited 34
6.6.4 Use with Caution 35
6.6.5 Concomitant Medication Reporting 35
7 ASSESSMENT PLAN 36
7.1 Schedule of Assessments 36
7.2 Details of Assessments 39
7.2.1 Clinical Assessment 39
7.2.2 Imaging 40
7.2.3 Health Related Quality of Life (HRQL) 40
7.2.4 Healthcare Resources 41
7.2.5 Blood Collection 41
7.2.6 Tissue Collection 41
7.3 Follow-Up after Treatment 42
8 OUTCOMES, ENDPOINTS AND OTHER MEASUREMENTS 42
8.1 Overall Survival (OS) 42
8.2 Progression Free Survival (PFS) 42
8.3 Objective Tumour Response Rate (OTRR) 42
8.4 Adverse Events 42
8.5 Health-Related Quality of Life (HRQL, EORTC QLQ-C30, QLQ-LC29, EQ-5D-5L) 42
8.6 Healthcare Resource Use 43
8.7 Incremental Cost Effectiveness 43
8.8 Tertiary/Correlative Measures 44
9 SAFETY REPORTING 44
9.1 Definitions 44
9.2 Recording Adverse Events 46
9.3 Pregnancy 46
9.3.1 Maternal Exposure 47
9.3.2 Paternal Exposure 47
9.4 Reporting of Serious Adverse Events (including SUSARs, SSIs and USMs) 47
10 CENTRAL REVIEW 48
10.1 Imaging 48
11 CENTRAL STORAGE OF BIOSPECIMENS 48
11.1 Central Tissue Collection 48
11.2 Central Blood Collection 48
12 STUDY TREATMENT SUPPLY AND ACCOUNTABILITY 48
12.1 Durvalumab 48
12.1.1 Formulation/Packaging/Storage 48
12.1.2 In Use Storage and Stability 48
12.2 Cisplatin/Carboplatin and Pemetrexed or Ipilimumab and Nivolumab 49
12.2.1 Formulation/Packaging/Storage 49
12.3 Supply 49
12.4 Drug Accountability 49
12.5 Background Treatment 49
13 STATISTICAL CONSIDERATIONS 49
13.1 Sample Size 49
13.2 Statistical Analysis 49
13.3 Interim Analyses 50
14 STUDY ORGANISATION and COMMITTEES 50
14.1 Study Coordination 50
14.2 International Trial Steering Committee 51

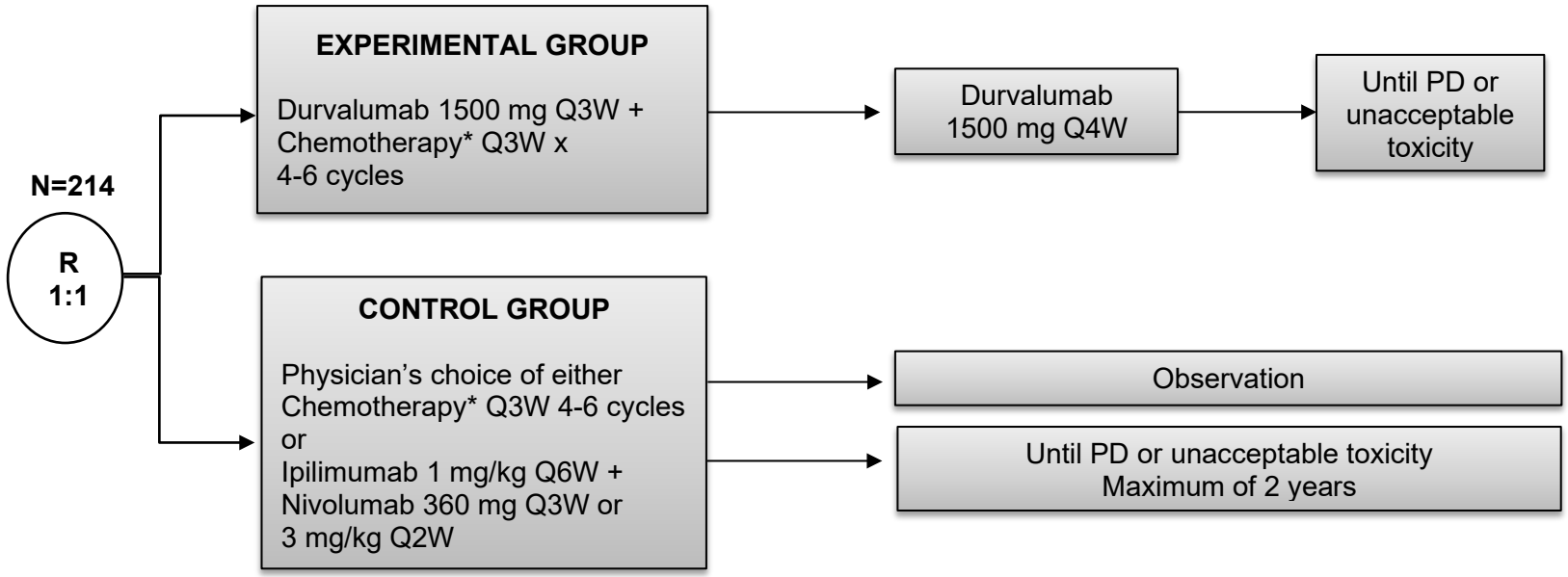
14.3 Independent Safety and Data Monitoring Committee (ISDMC) 51
15 ADMINISTRATIVE ASPECTS 51
15.1 Ethics and Regulatory Compliance 51
15.2 Confidentiality 51
15.3 Protocol Amendments 51
15.4 Data Handling and Record Keeping 52
15.5 Study Monitoring 52
15.6 Audit and Inspection 52
15.7 Clinical Study Report 52
15.8 Publication Policy 53
16 REFERENCES 54
17 APPENDICES 58
17.1 Appendix 1 Modified RECIST 1.1 Criteria for Pleural Mesothelioma 58
17.2 Appendix 2 ECOG Performance Status Scales 64
17.3 Appendix 3 Cockcroft-Gault Formula 65
17.4 Appendix 4 Acceptable Birth Control Methods 66
17.5 Appendix 5 Management of Immune-mediated Adverse Events (ImAEs), infusion-related reaction and non-immune related reactions 68
17.6 Appendix 6 Common Terminology Criteria for Adverse Events (CTCAE) 96
17.7 Appendix 7 iRECIST as applied to Pleural Mesothelioma 97
17.8 Appendix 8 EORTC QLQ-C30 100
17.9 Appendix 9 Euroqol 5 item preference-based measure of health (EQ-5D-5L) 104
17.10 Appendix 10 Ethics and Regulatory Compliance for USA Sites 106

1 SYNOPSIS AND SCHEMA

Background	First line chemotherapy in unresectable pleural mesothelioma (PM) consists of cisplatin/carboplatin and pemetrexed. This provides a median overall survival of 12.1 months, progression free survival (PFS) of 5.7months (PFS at 6 months (PFS6) of 48%) and a response rate of 41% (1). The majority of patients who do respond to first line therapy develop disease progression once therapy has stopped, and there is no accepted or approved second line therapy in this disease, nor a maintenance therapy that has been shown efficacious. A phase 2 single arm trial combining first line cisplatin, pemetrexed and durvalumab, a checkpoint inhibitor, showed encouraging activity, with PFS6 of 57% and response rate of 46%. Checkmate 743 showed longer overall survival with ipilimumab and nivolumab than with chemotherapy in non-epithelioid PM, but effects on overall survival were unclear in the larger subgroup with epithelioid PM. Protocol version 4 was therefore amended to: restrict accrual to epithelioid histology; change the control group treatment to physician's choice of either chemotherapy with a platinum and pemetrexed or immunotherapy with ipilimumab and nivolumab; and, change the randomisation ratio from 2:1 to 1:1.
Aim	To determine the effectiveness of chemo-immunotherapy with a platinum, pemetrexed, and durvalumab versus physician's choice of either chemotherapy with a platinum and pemetrexed or immunotherapy with ipilimumab and nivolumab.
Objectives Primary	To determine effects on 1. Overall survival
Secondary	2. PFS (by mRECIST 1.1 for PM and iRECIST) 3. Objective tumour response [(OTR) by mRECIST 1.1 for PM and iRECIST)] 4. Adverse events (CTCAE v5.0) 5. Health-related quality of life (HRQL, EORTC QLQ-C30, QLQ-LC29, EQ-5D-5L) 6. Healthcare resource use 7. Incremental cost-effectiveness
Tertiary and Correlative	8. To explore and validate potential prognostic/predictive biomarkers of clinical outcomes (including but not limited to candidates identified in the phase II DREAM and PrE0505 studies, PD-L1 expression, HLA type, T cell tumour infiltration, T cell receptor repertoire, tumour mutational burden, and gene signatures). 9. To collect an imaging databank for future validation of radiological response metrics in mesothelioma.
Design	Open label, randomised*, phase 3 trial stratified for: 1. Age (18-70 years versus older than 70) 2. Sex (male vs female) 3. Platinum chemotherapy (cisplatin or carboplatin) 4. Planned control regimen (chemotherapy or ipilimumab and nivolumab)** 5. Region (Australia/New Zealand vs USA vs other) *Randomisation ratio changed from 2:1 to 1:1 at amendment 4.0 ** Planned control regimen added at amendment 4.0

Population	Adults commencing first-line systemic treatment for unresectable epithelioid pleural mesothelioma; sarcomatoid and biphasic subtypes excluded following amendment 4.0.
Study treatments	Participants are randomly allocated in a ratio of 1:1 to either: 1. Experimental Group: Durvalumab 1500 mg every 3 weeks (Q3W) + chemotherapy* Q3W for 4 to 6 cycles, followed by durvalumab 1500 mg Q4W until disease progression or unacceptable toxicity 2. Control Group: Physician's choice of either a) Chemotherapy* Q3W for 4 to 6 cycles followed by observation OR b) Ipilimumab 1 mg/kg every 6 weeks (Q6W) and nivolumab 360 mg every 3 weeks (Q3W) or 3 mg/kg every 2 weeks (Q2W) until disease progression, unacceptable toxicity, or up to 2 years. *Chemotherapy: Cisplatin 75 mg/m² or carboplatin AUC 5 Q3W plus pemetrexed 500 mg/m² Q3W
Assessments	Clinical assessments before each cycle of treatment (i.e. 3 weekly). Imaging with CT scans and HRQL forms at baseline, then at weeks 6, 12, 18, 26, 34, 42, 50 and then every 12 weeks until disease progression. Blood samples for translational research studies of circulating biomarkers at baseline, day 1 of cycle 2, and day 1 of cycle 3.
Statistical considerations	480 participants recruited over 33 months and followed for another 18 months provides over 85% power if the true hazard ratio for overall survival was 0.70 with 2-sided alpha of 0.049, assuming a median survival of **18** months in the control group, **25.7** months in the experimental group, and an 8% allowance for lost to follow up/missing data. A single interim analysis will be conducted at least 6 months after the completion of recruitment when 50% of the required events have been observed, using the Lan-DeMets alpha spending function with an O'Brien-Fleming stopping boundary. Recruitment was closed with 214 participants.

Study Schema



Eligibility

- Advanced pleural mesothelioma (PM)
- Epithelioid histology
- Commencing first-line systemic treatment
- ECOG PS 0 or 1
- No prior systemic treatment/ RT to measurable lesions or radical surgical debulking

Stratification Factors

- Age (18-70 years vs > 70)
- Sex (male vs female)
- Platinum chemotherapy (cisplatin or carboplatin)
- Planned control regimen (chemotherapy or ipilimumab and nivolumab)
- Region (ANZ vs USA vs Other)

***Chemotherapy:** Cisplatin 75 mg/m² or carboplatin AUC 5 plus pemetrexed 500 mg/m²

2 Background

2.1 *Mesothelioma Epidemiology*

The incidence of pleural mesothelioma (PM) is still rising worldwide, particularly in Asia due to ongoing heavy asbestos use. For example, the estimated number of future cases for Japan alone is 66,000 in the upcoming decades; in China the numbers will be substantially more. In the UK and USA the expected number of cases in the next few decades are 65,000 and 85,000, respectively. Once diagnosed, this disease is nearly uniformly incurable and rapidly fatal, with a median survival of less than a year; systemic treatment with palliative intent is the only option (2-4). Hence, in the coming decades, many hundreds of thousands of people worldwide will require systemic treatment for mesothelioma. Access to treatment will increase with anticipated economic growth in countries which continue to use asbestos.

2.2 *Current Treatment Options in Mesothelioma*

Standard first line chemotherapy for advanced unresectable PM consists of 6 cycles of cisplatin and pemetrexed, which provides a survival benefit of approximately 3 months over cisplatin alone, and benefits to patient quality of life (1-4). A clinical trial of adding bevacizumab to cisplatin and pemetrexed demonstrated a survival benefit of 2 months over chemotherapy alone; however this combination was not approved by the US FDA or most other regulatory bodies (5). The addition of the multi-targeted tyrosine kinase inhibitor nintedanib to cisplatin and pemetrexed also demonstrated a progression free survival benefit in a randomised phase 2 trial, however a subsequent randomised phase -3 trial was negative (6). A substantial proportion of patients (approximately 1/3) decide to forgo systemic treatment, balancing potential side effects versus expected limited benefit (7). The Checkmate 743 trial showed a benefit for overall survival for combination ipilimumab and nivolumab over combination chemotherapy, however the benefits were most pronounced in those with non-epithelioid histology (further described in Section 2.5). The majority of patients that do respond to first line therapy develop disease progression once therapy has stopped, and there is no accepted or approved second line therapy in this disease, nor a maintenance therapy that has been shown efficacious. Thus, there is a strong unmet clinical need to improve current first line systemic therapy in mesothelioma.

2.3 *Durvalumab Background/Non-Clinical and Clinical Experience*

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1. The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor- elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ (8). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell dependent mechanism (8). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

As of the date cut-off (DCO) date of 12 July 2020, an estimated 9751 patients have received durvalumab in AstraZeneca or MedImmune-sponsored interventional studies in multiple tumour types, stages of disease and lines of therapy. Of these, 4337 patients received durvalumab monotherapy, 2438 patients received durvalumab in combination with tremelimumab, and 2976 patients received durvalumab in combination with an investigational and/or an approved product. An estimated 12768 patients have been randomised to the various treatment/comparator arms in sponsor-blinded and/or double-blinded studies. (Investigator's Brochure v16, 2020). Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

2.3.1 Overall Risks

Monoclonal antibodies directed against immune checkpoint proteins, such as programmed cell death ligand 1 (PD-L1) as well as those directed against programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor (ICI) 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 diarrhoea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism.

2.4 *AEs of Immune Checkpoint Inhibitors*

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

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 events (Appendix 5).

Durvalumab

AEs in combination of durvalumab with chemotherapy of the CASPIAN study (Study D419QC00001) are as follows., a total of 265 patients with SCLC have been treated with durvalumab in combination with chemotherapy (etoposide platinum [carboplatin or cisplatin]) in Study D419QC00001. AEs reported were consistent with the established safety and tolerability profile of durvalumab, and in keeping with AEs that are typically associated with etoposide platinum chemotherapy. (9)

Of the 265 patients, 260 (98%) had at least 1 AE (regardless of causality). The most common grade 3 or worse AEs were neutropenia (24%) and anaemia (9%). Serious AEs and AEs leading to discontinuation of at least one study drug were reported in 32% and 10% patients. Deaths due to AEs occurred in 6 patients (cardiac arrest, dehydration, hepatotoxicity, interstitial lung disease, pancytopenia, and sepsis [n=1 each]). Immune-mediated AEs were reported in 20% of patients, with the most common AESIs being Grade 1 or 2 hypothyroid and hyperthyroid events. Five percent had grade 3 or 4 immune-mediated AEs and 2 patients had deaths due to AESIs (hepatotoxicity and interstitial lung disease). (9)

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

Ipilimumab and Nivolumab

Among 300 participants treated with ipilimumab and nivolumab in the Checkmate 743 (10), the most frequent grade 1-2 AE (proportion of participants) were diarrhoea (17%), pruritus (15%), rash (13%), fatigue (13%), hypothyroidism (11%), and nausea (10%). The most frequent grade 3-5 AE were increased lipase (4%), diarrhoea (3%), colitis (2%), and increased amylase (2%).

2.5 *Rationale for Immune Checkpoint Blockade in Mesothelioma*

Mesothelioma has previously been shown to be amenable to immunotherapy, but with modest overall response rates. Initial phase II studies with the CTLA4 inhibitor given as second-line therapy to patients with mesothelioma gave durable partial responses in 7%, and disease control in 31% of patients (11, 12). However, unfortunately a subsequent randomised phase IIb trial (placebo vs tremelimumab) in the second line setting for this study did not demonstrate any survival benefit for tremelimumab (13).

Most importantly, in recent months, a number of small clinical trials have reported exciting single agent activity for PD pathway blockade, including PD1 and PD-L1 inhibition, as well as emerging results from trials combining PD pathway blockade with CTLA4 blockade. Results as available March 2019 are shown in Table 1.

Table 1: Recent Clinical Trials Results:

Trial	Keynote-028	Pembrolizumab (Kindler)	Nivo-Meso	JAVELIN meso cohort	MERIT (Japan)
Agent	Pembrolizumab	Pembrolizumab	Nivolumab	Avelumab	Nivolumab
PD-L1 selection?	✓	×	×	×	×
N patients	25	34	34	53	34
Prior therapy	92%	100%	100%	100%	100%
Responses					
CR	0%	0%	0%	0%	0%
PR	20%	21%	24%	9.4%	29%
SD	52%	59%	23%	47.2%	39%
PD	16%	20%	53%	34%	32%
Median PFS	5.4 months	6.2 months	2.6 months	3.9 months	6.1 months
Median OS	18 months	11.9 months	11.8 months	NR	NR

Mesothelioma also expresses PD-L1, which has been shown to correlate with response in patients with both melanoma and NSCLC when nivolumab is given as single agent. Consistent in a number of studies, around 40% of mesothelioma samples overexpress PD-L1 mRNA or on immunohistochemistry as compared to normal mesothelium (14-18). The expression of PD-L1 in mesothelioma is a negative prognostic factor, and it appears to be more commonly expressed in those with the more aggressive sarcomatoid histology (14, 16). However, to date, the expression levels of PD-L1 do not appear to be related to response to checkpoint blockade, with the caveat that most biopsies have been archival, in patients who have subsequently received treatment, and are generally from one site only in a large tumour.

Combination immunotherapy appear more additive than synergistic, and potentially expose patients to substantial toxicities of dual immunotherapy. Table 2 summarises these results as of July 2022. In the Checkmate 743 study, OS benefit of nivolumab-ipilimumab combination vs chemotherapy was greater in patients with tumours with PD-L1 expression of 1% or higher, than those in of less than 1% (10). The details of this study is outlined in Section 2.6. The INITIATE study also performed a posthoc subset analysis by PD-L1 expression, suggesting improved patient outcomes with higher levels of PD-L1 expression in both tumour and infiltrating immune cells.

Table 2: Combination Treatment Clinical Trial Results:

Trial	Checkmate 743 (10)		MAPS-2 (5)		NIBIT-Meso (19)	INITIATE) (20)
Agent	Nivolumab + Ipilimumab vs chemotherapy		Nivolumab + Ipilimumab vs Nivolumab		Tremelimumab + Durvalumab	Nivolumab + Ipilimumab
PD-L1 selection?	×		×		×	×
N patients	303	302	62	63	40	34
Prior therapy	No		No		Some	No
Responses			Combo	Nivo		
CR	2%	0%	0%	0%	0%	0%
PR	38%	43%	28%	19%	28%	29%
DCR	77%	85%	52%	40%	65%	68%
PD	18%	5%	42%	59%	35%	32%
Median PFS	6.8 months	7.2 months	5.6 months	4.0 months	5.7 months	6.2 months
Median OS	18.1 Months	14.1 months	15.9 months	11.9 months	16.6 months	Not reached

2.6 *First Line Dual Immune Checkpoint Blockade*

Checkmate 743, a randomised, phase 3 trial that compared dual immunotherapy with ipilimumab and nivolumab versus chemotherapy with a platin plus pemetrexed, showed improved OS among all participants randomised (HR 0.74; 95% CI 0.60-0.91; p=0.002) (10). However, the OS benefit was predominantly observed in the 25% of participants with non-epithelioid histology (HR 0.46, 95% CI 0.31-0.68), rather than the 75% with epithelioid histology (HR 0.86, 95% CI 0.69-1.08). PFS and objective tumour response rates were similar with ipilimumab and nivolumab versus chemotherapy. While extensive biomarker characterisation is planned, only analysis by PD-L1 expression is available to date. Immunohistochemistry on archival or fresh tissue used the 28-8 pharmDx assay and assessed the proportion of tumour cells showing plasma membrane staining of any intensity. A pre-planned subgroup analysis using a pre-specified cut-point of 1% for PD-L1 expression showed no difference in OS between treatment groups in the 23% of participants with tumour PD-L1 expression <1%, whereas among the 77% with PD-L1 expression ≥ 1%, OS was longer with ipilimumab and nivolumab than chemotherapy (HR 0.69, (95% CI 0.55-0.87). The most important outstanding issue from CheckMate 743 is the identification of patients with epithelioid mesothelioma most likely to benefit from combination immunotherapy. A more nuanced analysis of PD-L1 expression may improve our understanding of the biology of response, but is not yet available.

2.7 *Rationale for Combining Cisplatin/Pemetrexed Chemotherapy with Immune Checkpoint Blockade*

Until recently, the consensus was that immunotherapeutic approaches could not be combined with cytotoxic chemotherapy. But findings from our group and others have unequivocally shown that chemotherapeutics can have immune-stimulating properties (21-28). In particular for platinum-based chemotherapy many beneficial immunological effects have been identified. These immunogenic effects include modulation of STAT signalling (29, 30) induction of an immunogenic type of cancer cell death through exposure of calreticulin and release of ATP and high-mobility group protein box-1 (HMGB-1) (31-33); and enhancement of the effector immune response through modulation of and mannose-6-phosphate receptor expression (34). We have shown that platinum-based chemotherapeutics downregulate PD-L1 and PD-L2 expression on both antigen-presenting cells and tumour cells, resulting in increased T cell activation and tumour cell recognition (29, 35).

Clinical studies have aimed to identify potential immune checkpoint (IO)/platinum-based chemotherapy combinations in non-small-cell lung cancer (NSCLC), SCLC, breast and head and neck squamous cell cancer (HNSCC). Multiple phase II and III trials have demonstrated combination of IO and chemotherapy showed better efficacy compared to chemotherapy alone. A large phase III trial investigated the efficacy of adding atezolizumab (a PD-L1 inhibitor) to chemotherapy (carboplatin plus paclitaxel) with bevacizumab (IMPower 150) in patients with advanced non-squamous NSCLC without prior systemic therapy. In the 692 patients who had wild-type EGFR genotype, the median PFS was longer in the combination IO and chemotherapy group vs chemotherapy alone (8.3 months vs. 6.8 months; HR 0.62 (95% CI 0.52-0.74; p<0.001). The median OS was also longer in the combination group (19.2 months vs 14.7 months; HR 0.78; 95% CI 0.64-0.96; p=0.02).

A randomised, phase 2 trial (Keynote 021) of carboplatin plus pemetrexed with pembrolizumab showed significant better RR and longer PFS compared to chemotherapy alone in first line treatment for advanced NSCLC. Based on this study, FDA has approved frontline pembrolizumab in combination with carboplatin and pemetrexed in advanced NSCLC irrespective of PD-L1 status. The phase III study (Keynote 189) randomly assigned 616 non-squamous NSCLC patients without sensitising mutations, in 2:1 ratio to platinum and pemetrexed with either pembrolizumab (a PD-1 inhibitor) or placebo in the first line setting. In the intention-to-treat (ITT) population, the estimated 12 month OS was 69.2% vs 49.4% (IO+chemotherapy vs chemotherapy) with improvement of OS seen across all PD-L1 categories. Median PFS was 8.8 months vs. 4.9 months and RR was 47.6% vs 18.9% (36). Hence, pemetrexed/cisplatin is a reasonable partner combination with immunotherapy.

More recently, longer overall survival were also shown in a phase III RCT (Keynote 407) in advanced squamous NSCLC with combination of carboplatin, taxane and pembrolizumab vs chemotherapy (HR OS 0.64, 95% CI 0.49-0.85, p=0.0008, ASCO presentation 2018); SCLC (ImPower 133) with combination of first line platinum-based chemotherapy and atezolizumab vs chemotherapy (HR OS 0.7, 95% CI 0.54-0.91, p=0.007) and HNSCC (Keynote 048) with combination of first line platinum chemotherapy with pembrolizumab vs chemotherapy plus cetuximab (HR2+ OS, 0.77, 95% CI 0.63-0.93, p=0.0034; ESMO presentation 2018) (37).

Maintenance treatment using durvalumab, a PD-L1 inhibitor has been validated in the recently reported PACIFIC trial. This was a phase III trial which randomised patients with stage III NSCLC to either durvalumab or placebo post chemoradiotherapy. Both the primary co-endpoints of OS and PFS were met, with durvalumab prolonging OS (HR 0.68, 95% CI 0.47-0.997, p=0.0025) and PFS (HR 0.51, 95% CI 0.41-0.63).

These are strongly positive studies for overall survival endpoints, which are likely to change the standard of care in these settings. There are other studies combining IO and chemotherapy currently underway in NSCLC, including BR34 (durvalumab/tremelimumab plus chemotherapy) and Checkmate 227 (nivolumab/ipilimumab and chemotherapy vs nivolumab and chemotherapy vs chemotherapy)(38) .Overall survival is regarded as the most robust end point for immunotherapy trials due to the observed ‘tail on the curve’ of long term survival in many of these studies.

2.8 *Results from the Single Arm ‘DREAM’ Clinical Trial*

The Thoracic Oncology Group of Australasia (TOGA) completed accrual to the phase 2, single-arm DREAM clinical trial in October 2017, combining durvalumab (1125 mg q3w) with cisplatin and pemetrexed as first line therapy for unresectable pleural mesothelioma. Six patients were treated in a safety lead-in phase, with no dose limiting toxicities observed over two cycles of triple combination treatment in each of these first six patients. The trial continued to recruit 54 patients, and completed accrual at 10 Australian sites over less than 10 months (including 2 months for initial safety lead in). The baseline characteristics are included in Table 3. 30 of 54 patients (56%) received 6 cycles of cisplatin. 13 patients (24%) converted to carboplatin. The median number of durvalumab doses was 11.5 (range 1-18). Dose intensity of cisplatin was 97%; dose intensity of pemetrexed was 94%, dose intensity of durvalumab was 94%.

Table 3: Baseline Characteristics of DREAM:

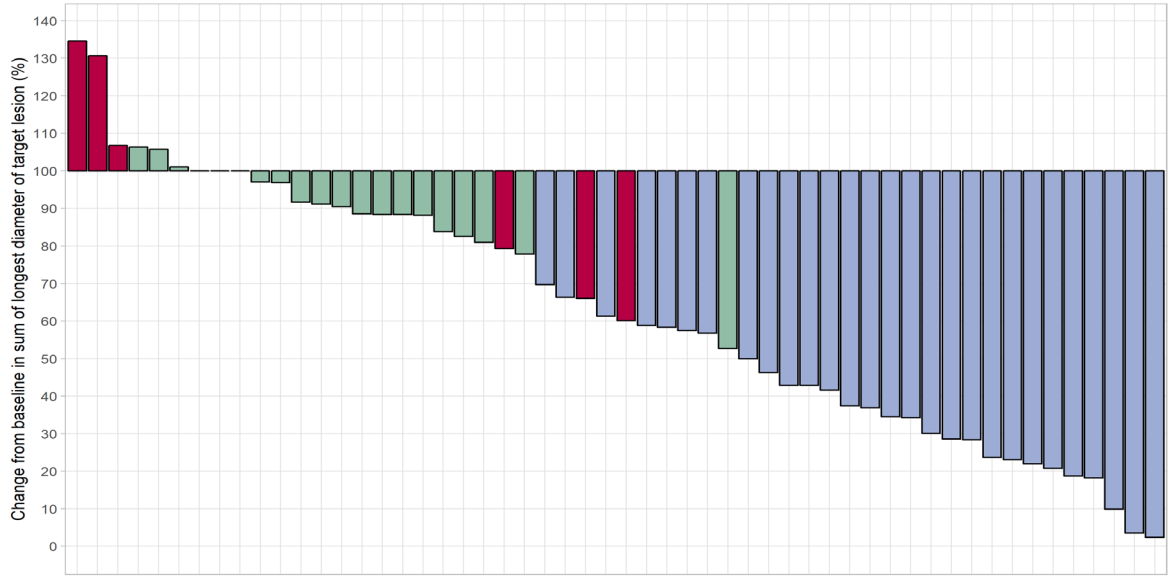
Characteristic	N=54
Age (years)	68 (42-82)
Sex male	45 (82%)
ECOG 0	33 (60%)
Epithelioid histology	45 (82%)
Prior radiotherapy	5 (9%)
Prior non-radical surgery	5 (9%)

The final result of this study was reported in Lancet Oncology . The primary endpoint of PFS6 was met, showing 57% of a total of 54 patients had not progressed at 6 months. The median PFS by mRECIST was 6.9 months (95% CI 5.5-9.0), by iRECIST was 7.0 months (95% CI 5.7- 9.0) and overall survival was 18.4 months (95% CI 12.6-not defined). These results for objective radiological response are exciting (Table 4), and importantly, with many patients continuing on therapy and having only reached one imaging time point, there is potential for objective radiological responses to deepen. Many of these patients also had deep and long duration of responses. The median OS was 18.4 months (95% CI 13.1 months – 24.8). These exciting results have prompted TOGA and PrECOG to propose a randomised phase III clinical trial to confirm the clinical importance of these findings. Correlative laboratory work is currently underway. There was no correlation between the proportion of tumour cells or total cells expressing PD-L1 on archival tumour tissue and progression-free survival.

Table 4: Objective Tumour Response Rate in DREAM

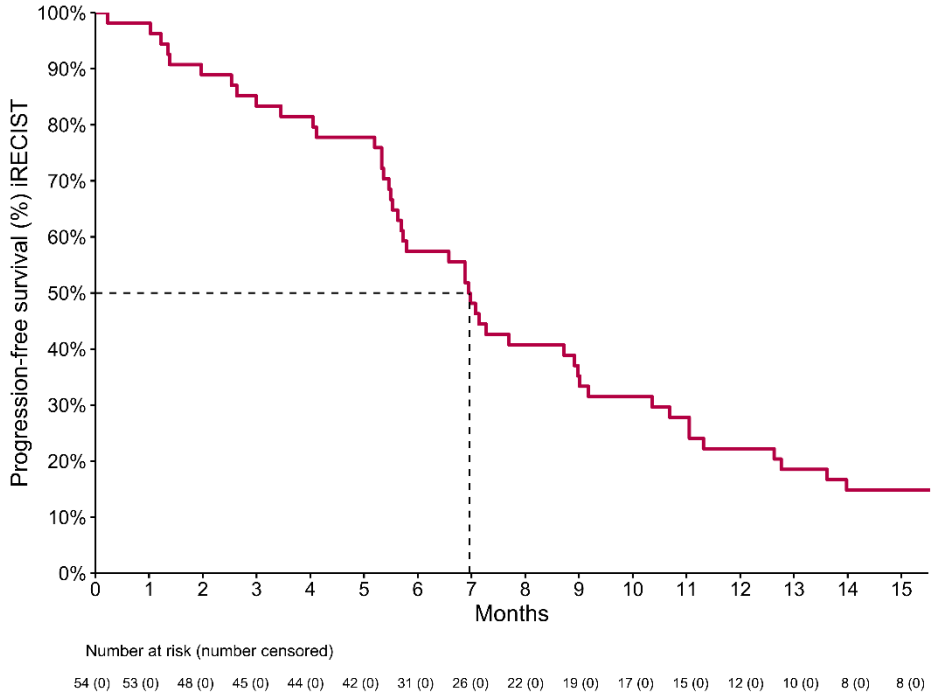
	Confirmed Response mRECIST (%)	Confirmed Response iRECIST (%)
Complete response	0	0
Partial response	26 (48)	26 (48)
Stable disease	21 (39)	22 (41)
Progressive disease	7 (13)	6 (11)
Total	54	54

Figure 1: Waterfall Plot of Objective Radiological Responses by mRECIST from DREAM



Red= PD, green = SD, blue= PR

Figure 2: Kaplan Meier plot of Progression Free Survival from DREAM



2.9 *Results from the Single Arm "PrE0505" Clinical Trial*

Given the role of inflammation in PM and promising responses to PD-1 pathway blockade in pre-treated PM, PrECOG also conducted a phase 2 single arm study of the anti-PD-L1 antibody, durvalumab (durva), combined with cisplatin or carboplatin/pemetrexed (CP) for patients with untreated PM of any subtype.

Eligible patients were treatment-naïve with surgically unresectable PM. The primary endpoint was overall survival (OS); patients received up to 6 cycles of durva-CP, followed by maintenance durva for up to 1 year. Carboplatin was permitted for patients with baseline hearing or renal impairment. The first 15 patients were monitored for dose-limiting toxicities (DLTs). Secondary endpoints included toxicity, objective response by modified RECIST, progression-free survival (PFS). Correlative endpoints were exploratory. With a sample size of 55 patients and 32 events, the study had 90% power to detect a 58% improvement in median OS from 12 months (historical control) to 19 months with durva-CP.

PrE0505 enrolled 55 patients at 15 US-based sites between 06/2017 and 06/2018. Histologic subtypes were epithelioid (75%), biphasic (11%), sarcomatoid (13%), and desmoplastic (2%). There were no DLTs during the run-in period.(39)

As of April 24, 2020, the median follow up was 24.2 months and 33 deaths occurred. The median OS at the time of report was 20.4 months. The estimated percentages of patients alive at 6, 12 and 24 months were 87.2%, 70.4% and 44.2% respectively. Patients with epithelioid PM had significantly longer median OS than historical control (24.3 months vs. 9.2 months, hazard ratio-HR: 0.27, 95% CI: 0.13- 0.57, p<0.001). (39, 40)

Correlative analyses for this study are ongoing. Exome sequencing, TCR sequencing and dual PD-L1/CD8 staining were completed on baseline tumors from at least 45 of the 55 patients enrolled as well as RNA sequencing for those with adequate tissue. Initial results show that tumors harbored an average tumor mutation burden of 22 somatic sequence alterations and varying levels of aneuploidy were detected.

The combination of chemotherapy with durvalumab delivered a promising median OS in these patients with previously untreated unresectable PM. Full results from the study along with the correlative analyses performed will be reported once the study reaches full maturation.

2.10 *Rationale for Fixed Dosing*

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

Similar findings have been reported by others. (41-44) Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies. (43) In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in pharmacokinetic/pharmacodynamics parameters. (44)

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

During chemotherapy, a Q3W fixed dosing regimen will be used to align with the 3QW chemotherapy regimen. Pharmacokinetic/pharmacodynamics parameters indicate that the Q3W fixed dosing regimen is also safe and efficacious.

2.11 *Rationale for this Trial*

Preliminary data suggests that the addition of durvalumab to cisplatin/carboplatin and pemetrexed results in an increased proportion of radiological responses, longer progression free survival, and substantially longer overall survival than would be observed with cisplatin/carboplatin and pemetrexed alone. (45) However, the addition of durvalumab treatment may increase health system costs. Hence, this clinical trial aims to further evaluate the potential for improved patient outcomes and cost-effectiveness with this combination.

Overall, preliminary safety and efficacy data from the DREAM study suggest a favourable risk-benefit profile for this combination, with further evidence required to confirm this in the DREAM3R randomised clinical trial.

In response to the results of Checkmate 743 (10), Protocol version 4 was amended to: restrict accrual to epithelioid histology; change the control group treatment to physician's choice of either chemotherapy with a platinum and pemetrexed or immunotherapy with ipilimumab and nivolumab; and, change the randomisation ratio from 2:1 to 1:1.

3 AIM AND OBJECTIVES

To determine the effectiveness of chemo-immunotherapy with a platinum, pemetrexed, and durvalumab versus physician's choice of either chemotherapy with a platinum and pemetrexed or immunotherapy with ipilimumab and nivolumab.

The specific objectives (endpoints) of this trial are to determine:

Primary Objectives	**1.** Effects on overall survival
Secondary Objectives	**2.** PFS (by mRECIST 1.1 for PM and iRECIST) **3.** Objective tumour response [(OTR) by mRECIST 1.1 for PM and iRECIST] **4.** Adverse events (CTCAE v5.0) **5.** Health-related quality of life (HRQL, EORTC QLQ-C30, QLQ LC-29, EQ-5D-5L) **6.** Healthcare resource use **7.** Incremental cost-effectiveness
Tertiary and Correlative Objectives	**8.** To explore and validate potential prognostic/predictive biomarkers of clinical outcomes, (including but not limited to candidates identified in the phase II DREAM and PrE0505 studies, PD-L1 expression, HLA type, T cell tumour infiltration, T cell receptor repertoire, tumour mutational burden and gene signatures). **9.** To collect an imaging databank for future validation of radiological response metrics in mesothelioma.

4 DESIGN

Open label, randomised phase 3 trial.
Participants will be allocated to one of the two treatment groups in a ratio of 1:1* experimental (durvalumab + chemotherapy) or control (chemotherapy or ipilimumab and nivolumab) by a central randomisation system that stratifies for:

1. Age (18-70 years vs older than 70)
2. Sex (male vs female)
3. Platinum chemotherapy (cisplatin or carboplatin)
4. Planned control regimen (chemotherapy or ipilimumab and nivolumab)**
5. Region (Australia/New Zealand vs USA vs other)

*Randomisation ratio changed from 2:1 to 1:1 at amendment 4.0
** Planned control regimen added at amendment 4.0

5 STUDY POPULATION

Patients must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial. No exceptions will be made to these eligibility requirements at the time of registration. All enquiries about eligibility should be addressed by contacting the NHMRC CTC or regional study medical monitor prior to registration.

US sites also please refer to Appendix 10: Ethics and Regulatory Compliance for USA Sites.

5.1 *Target Population*

Adults commencing first-line systemic treatment for unresectable epithelioid pleural mesothelioma; sarcomatoid and biphasic subtypes excluded following amendment 4.0.

5.2 *Inclusion Criteria*

1. Adults (18 years or over) with a histological diagnosis of epithelioid pleural mesothelioma that is not amenable to curative surgical resection. Histological diagnosis requires tumour tissue from an open biopsy, or a core biopsy with a needle of 19 gauge or wider.
2. Measurable disease as per modified RECIST 1.1 (mRECIST 1.1) criteria for assessment of response in pleural mesothelioma (Appendix 1 - Modified RECIST 1.1 Criteria for Assessment of Response in Pleural Mesothelioma and Radiology Manual), without prior radiotherapy to these sites.
3. Body weight >30kg.
4. ECOG performance status of 0 or 1 (Appendix 2 – ECOG Performance Status Scales)
5. Tumour tissue (Formalin-Fixed Paraffin-Embedded [FFPE]) available from standard of care diagnostic biopsy for PD-L1 testing and other correlative biomarker testing at a central laboratory.
6. Life expectancy of at least 12 weeks.
7. Adequate blood tests (done within 14 days prior to randomisation) and with values within the ranges specified below. Blood transfusions are permissible if completed at least 7 days prior to treatment start.
   - Haemoglobin ≥ 9.0 g/L
   - Absolute neutrophil count ≥ 1.5 x 10^9/L
   - Platelets ≥ 100 x 10^9/L
   - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) (except participants with Gilbert's Syndrome, who are eligible with bilirubin ≤ 2.5 ULN)
   - Alanine transaminase ≤ 2.5 x upper limit of normal (ULN), unless liver metastases or invasion are present, in which case it must be ≤ 5 x ULN
   - Aspartate aminotransferase ≤ 2.5 x ULN, unless liver metastases or invasion are present, in which case it must be ≤ 5 x ULN
   - Creatinine clearance (CrCl) ≥ 45 mL/min (use Cockcroft-Gault formula as per Appendix 3)

     NOTE: Carboplatin AUC 5 must be the initial platinum agent of choice in patients with creatinine Cl <60 mL/min but ≥ 45 mL/min, or those with clinically reported hearing loss.
8. Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient or legal representative must sign a consent form prior to enrolment in the trial to document their willingness to participate.
9. Willing and able to comply with all study requirements, including treatment, timing and/or nature of required assessments.
10. Women of childbearing potential must use a reliable means of contraception during treatment and for at least 90 days thereafter. Breastfeeding is not permissible during or for at least 90 days after the final study treatment. Men must have been surgically sterilised or use a (double if required) barrier method of contraception if they are sexually active with a woman of child bearing potential (see Appendix 4 - Acceptable birth control methods).
11. Evidence of post-menopausal status or negative serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. (Appendix 4 - Acceptable birth control methods).

5.3 *Exclusion Criteria*

1. Non-epithelioid histology (biphasic or sarcomatoid).
2. Prior chemotherapy or other systemic anti-cancer or immunotherapy for PM.
3. Diagnosis based only on cytology or aspiration biopsy with a needle narrower than 19 gauge.
4. 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:
    a. Patients with vitiligo or alopecia
    b. Patients with hypothyroidism (e.g. following Hashimoto syndrome) stable on hormone replacement
    c. Any chronic skin condition that does not require systemic therapy
    d. Patients without active disease in the last 5 years may be included
    e. Patients with celiac disease controlled by diet alone
5. Any condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent dose of an alternative corticosteroid) or other immunosuppressive medications within 28 days of durvalumab or ipilimumab or nivolumab administration. Intranasal, inhaled or topical steroids or local steroid injections (e.g. intra-articular injection) are permitted in the absence of active autoimmune disease. Standard steroid premedication given prior to chemotherapy or as prophylaxis for imaging contrast allergy should not be counted for this criterion.
6. Participants with symptomatic or uncontrolled brain metastases or leptomeningeal disease are excluded.
7. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T cell co-stimulation or immune checkpoint pathways.
8. Current treatment or treatment within the last 12 months with any investigational anti-cancer products.
9. Concurrent enrolment in another clinical trial testing an anticancer treatment.
10. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 470 msec in screening ECG measured using standard institutional method or history of familial long QT syndrome.
11. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of study treatment on protocol. Note: Local surgery of isolated lesions for palliative intent is acceptable. Limited pleural biopsy procedures do not apply.
12. No other malignancy that requires active treatment. Participants with a past history of adequately treated carcinoma in situ, non-melanoma skin cancer or lentigo maligna without evidence of disease or superficial transitional cell carcinoma of the bladder are eligible.
13. Hearing loss or peripheral neuropathy considered by the investigators to contraindicate administration of either cisplatin, carboplatin or pemetrexed.
14. History of allergy or hypersensitivity to investigational product, cisplatin, carboplatin, pemetrexed, ipilimumab, nivolumab or any excipient.
15. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive cardiac failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, active peptic ulcer disease or gastritis, serious chronic gastrointestinal conditions associated with diarrhoea, active bleeding diatheses.
16. Hepatitis B, hepatitis C or human immunodeficiency virus (HIV). Exceptions include past or resolved Hepatitis B (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) and patients positive for hepatitis C (HCV) antibody if polymerase chain reaction is negative for HCV RNA. HIV testing is not required in absence of clinical suspicion of HIV.
17. Known history of primary immunodeficiency, allogeneic organ transplant, pneumonitis or active tuberculosis.
18. Receipt of live attenuated vaccination within 30 days prior to enrolment or within 30 days of receiving durvalumab, ipilimumab or nivolumab.
19. Specific comorbidities or conditions or concomitant medications which may interact with the investigational product(s).
20. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.

21. Serious medical or psychiatric conditions or social situation that might limit compliance with study requirements, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

5.4 *Study Enrolment*

Study enrolment process entails screening for participants, followed by randomisation for those who are eligible for the trial.

5.4.1 Screening

Written informed consent must be signed and dated by the participant, and signed and dated by the Investigator, prior to any study-specific screening investigations being performed. All patients who sign a consent will have screening data entered into the clinical database and will be assigned a study ID. Patients who don't meet eligibility will have no further data entered.
US sites also please refer to Appendix 10: Ethics and Regulatory Compliance for USA Sites

5.4.2 Randomisation

Randomisation must be performed according to the instructions in the Study Manuals. The allocation will be performed using the Medidata system and will be configured to use stratified permuted blocks (of random length 4 and 8). Stratification will be by age at randomisation (18-70 years vs older than 70), sex (male vs female), platinum drug (cisplatin vs carboplatin), planned control regimen (chemotherapy vs ipilimumab and nivolumab) and region (Australia/New Zealand vs USA vs other). Requests for randomisation will only be accepted from authorised investigators at sites that have all requisite approvals in place. Randomisation should be done only after all screening assessments have been performed and the responsible investigator has verified the participant's eligibility. Investigator must nominate control group treatment (platinum chemotherapy [carboplatin/cisplatin] or ipilimumab and nivolumab prior to randomisation).
Participants must be randomised before starting study treatment. Treatment should be planned to start as soon as possible but **within 7 days** after randomisation.
Once the randomisation process has been completed, the participant will be assigned a treatment group and written confirmation of successful randomisation will be provided to the site.
Individuals may only be randomised once in this trial.

6 TREATMENT PLAN

6.1 *Treatments*

Participants are randomly allocated in a ratio of 1:1 to either:

Experimental Group: Durvalumab 1500 mg Q3W + chemotherapy* Q3W for 4 to 6 cycles, followed by durvalumab 1500 mg Q4W until disease progression or unacceptable toxicity

Control Group: Physician's choice of either
a) Chemotherapy* Q3W for 4 to 6 cycles followed by observation
OR
b) Ipilimumab 1 mg/kg Q6W and nivolumab 360 mg Q3W or 3 mg/kg Q2W until disease progression, unacceptable toxicity, or up to 2 years.

*Chemotherapy: Cisplatin 75 mg/m² or carboplatin AUC 5 Q3W plus pemetrexed 500 mg/m² Q3W

Table 5: Experimental Group Study Treatments

Agent (s)	Dose	Route	Duration	Schedule	Frequency	
Cisplatin OR Carboplatin	75 mg/m^2 OR AUC 5	IV	Per institution practice	Day 1 each cycle	Every 3 weeks x 4 to 6 cycles	
Pemetrexed	500 mg/m^2	IV	Per institution practice	Day 1 each cycle	Every 3 weeks x 4 to 6 cycles	
Durvalumab	1500 mg	IV	60 minutes	Day 1 each cycle	Every 3 weeks	
Followed by Maintenance						
Durvalumab	1500 mg	IV	60 minutes	Day 1 each cycle	**Every 4 weeks**	Until disease progression/ unmanageable toxicity/ withdrawal of consent

Table 6. Control Group Study Treatments

Agent (s)	Dose	Route	Duration	Schedule	Frequency	
Cisplatin OR Carboplatin	75 mg/m^2 OR AUC 5	IV	Per institution practice	Day 1 each cycle	Every 3 weeks x 4 to 6 cycles	
Pemetrexed	500 mg/m^2	IV	Per institution practice	Day 1 each cycle	Every 3 weeks x 4 to 6 cycles	
Followed by close observation per standard of care						
<u>OR</u>						
Nivolumab	360 mg	IV	30 minutes	Day 1 each cycle	Every 3 weeks	Up to 2 years Or Until disease progression/ unmanageable toxicity/ withdrawal of consent
	3 mg/kg				Every 2 weeks	
Ipilimumab	1 mg/kg	IV	30 minutes	Day 1 each cycle	Every 6 weeks	
Followed by close observation per standard of care						

Note: 1 cycle of ipilimumab and nivolumab = 6 weeks
Ipilimumab and nivolumab control regimen added at amendment 4.0

Chemotherapy
See Section 6.3 for choice of platinum chemotherapy
It is recommended that cisplatin/carboplatin and pemetrexed be administered before durvalumab. Durvalumab will be administered immediately following or during the final hydration IV fluid bag for cisplatin/carboplatin administration.
In the absence of toxicity precluding chemotherapy (e.g. cumulative neuropathy, hearing impairment, kidney impairment) then it is recommended to continue chemotherapy up to a maximum of 6 cycles. However after the patient has completed 4 cycles it is up to the judgement of the site investigator whether to complete out the full 6 cycles.
If chemotherapy is stopped prior to completion of 6 cycles- in patients who are stable or responding to treatment if clinically indicated in the opinion of the investigator, continued durvalumab is permissible.
For patients entering into the maintenance stage, the first dose of durvalumab should commence 3 weeks after the last dose of chemo-durvalumab. Subsequent treatments with durvalumab will continue at 1500 mg on Day 1 on a **4-weekly schedule** in the absence of unequivocal disease progression, unacceptable toxicity, withdrawal of consent, or other reasons for discontinuation.

6.2 *Durvalumab*

6.2.1 Durvalumab Administration

Patients in the durvalumab + chemotherapy treatment group will receive 1500 mg durvalumab via IV infusion Q3W for 4-6 doses/cycles and then ongoing 1500 mg durvalumab via IV infusion Q4W thereafter until confirmed disease progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. (If a patient's weight falls to 30 kg or below (≤ 30 kg) the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q3W or Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q3W or Q4W).

Preparation of durvalumab doses for administration with an IV bag
The dose of durvalumab for administration must be prepared by the site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

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

A dose of 1500 mg (for patients >30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30.0 mL (i.e. 1500 mg) of durvalumab to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.
If weight falls to ≤ 30 kg weight-based dosing at 20 mg/kg will be administered using an IV bag containing 0.9% (weight/volume [w/v]) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter.
Standard infusion time 1 hour, however in the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.
Do not co-administer other drugs through the same infusion line.
The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered.
If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

6.2.2 Monitoring of Durvalumab Dose Administration

Please refer to Section 7.2.1 Clinical Assessment.

6.2.3 Durvalumab Dose Delay and Management of Treatment Related Adverse Events

No dose reductions and/or dose escalations of durvalumab are permitted.
Durvalumab may be delayed for up to 12 weeks. If no discontinuation criteria are met during this time, durvalumab may be recommenced. Any delay of 12 weeks or more would meet the criteria to discontinue durvalumab permanently.
In the event of a ≤ Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤ Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued. The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature (otherwise requires new infusion preparation).
The management of infusion-related reaction is summarised in Appendix 5 - Management of Immune-mediated Adverse Events (ImAEs), infusion-related reaction and non-immune related reaction.
For participants randomised to receive durvalumab, if durvalumab alone requires delay, chemotherapy should be continued on the usual planned date (provided there is no contra-indication). Restart durvalumab at the next scheduled dose per Appendix 5 - Management of Immune-mediated Adverse Events (ImAEs), infusion-related reaction and non-immune related reaction. If chemotherapy needs to be delayed due to drug related toxicity/AE, withhold **both chemotherapy and durvalumab** until chemotherapy retreatment criteria are met and restart both at the same time.

6.2.3.1 Haematological Criteria for Retreatment with Durvalumab on First Post-Chemotherapy Cycle

For participants randomised to receive durvalumab, for the first cycle of durvalumab following cessation of chemotherapy, durvalumab treatment may be administered on schedule if haematological toxicity of less than grade 3 is present.

6.2.4 Criteria to Discontinue Durvalumab Permanently

An individual participant will not receive any further durvalumab if any of the following occur in the participant in question:

a. Any treatment delay of 12 weeks or longer.
b. The investigator determines that continuation of treatment is not in the patient's best interest.
c. Occurrence of an exclusion criterion affecting patient safety, e.g. pregnancy or psychiatric illness.
d. Required use of a concomitant treatment that is not permitted, as defined in Section 6.6.
e. The patient declines further study treatment, or withdraws their consent to participate in the study.
f. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing.
g. Any AE that meets criteria for discontinuation as defined in Section 6.2.3.
h. Participant noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal, e.g. refusal to adhere to scheduled assessments.
i. Initiation of alternative anticancer therapy including another investigational agent.

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

Imaging Follow-Up

- **NOTE.** A patient who was receiving durvalumab and is deemed to be clinically benefiting despite initial progression (e.g. unconfirmed progression in the event of suspected pseudoprogression) may continue durvalumab at the discretion of the treating investigator. In this case, a confirmatory follow-up scan at least 4 weeks, but no longer than 8 weeks later is warranted per iRECIST.
- Patients who are permanently discontinued from further receipt of durvalumab, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter follow-up (see 7.1 Schedule of Assessments).
- Patients who permanently discontinue drug for reasons other than objective RECIST disease progression should continue to have RECIST scans performed q8w ±1w until week 50 (relative to the date of randomization), and then q12w ±1w thereafter until mRECIST 1.1 for PM-defined radiological PD plus an additional follow-up scan or death (whichever comes first) as defined the 7.1 Schedule of Assessments.
- If a patient is discontinued for mRECIST 1.1 for PM-defined progression, then the patient should have 1 additional follow-up scan performed at the next scheduled imaging visit, and no less than 8 weeks after the prior assessment of PD.

Participants who permanently discontinue durvalumab will be followed for safety as per Sections 7.1, 7.2 and 9.2 including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the participant is lost to follow-up or receiving subsequent anticancer treatment. All participants will be followed for survival. Participants who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.
The reasons for discontinuing treatment will be documented in the participant's medical record and eCRF.
If a participant wishes to stop the study assessments, they will be requested to allow their ongoing health status to be periodically reviewed via continued study visits or phone contact or from their general practitioner, or medical records, state-based cancer registries and/or the national mortality registry (AIHW).
Mortality data and other information may be collected for patients lost to follow-up from administrative data and other sources, e.g. Medicare, Health Insurance Commission and the Australian Institute of Health and Welfare in Australia; and similar sources in the USA.

6.3 *Cisplatin/Carboplatin and Pemetrexed*

Participants will receive 4-6 cycles of cisplatin or carboplatin and pemetrexed in the absence of progression, unacceptable toxicities or discontinuation from the study.
Carboplatin AUC 5 **must** be the initial platinum agent of choice in patients with creatinine Cl <60 mL/min but ≥ 45 mL/min. In addition, participants who commence cisplatin but experience cisplatin-related toxicities, such as hearing loss, grade 3 nausea or vomiting, or other indications as per the investigator, may be changed to carboplatin as per institutional practice and investigator discretion, and continued on the study. Once carboplatin is substituted for cisplatin, patients cannot change back to cisplatin.
In the absence of toxicity precluding chemotherapy (e.g. cumulative neuropathy, hearing impairment, kidney impairment) then it is recommended to continue chemotherapy up to a maximum of 6 cycles. However after the patient has completed 4 cycles it is up to the site investigator whether to complete out the full 6 cycles.

6.3.1 Cisplatin/Carboplatin and Pemetrexed Dose Administration

The starting dose of pemetrexed is 500 mg/m^2 administered as an intravenous infusion over approximately 10 minutes on day 1 of each 21-day cycle, followed by cisplatin 75 mg/m^2 or carboplatin AUC 5* (per Calvert formula) as an intravenous infusion (per standard institution timing)

approximately 30 minutes after pemetrexed administration. Pemetrexed and cisplatin dosing should use the DuBois formula for calculation of body surface area (BSA). Participants should receive adequate anti-emetic treatment and hydration before and/or after receiving cisplatin/carboplatin in accordance with their standard protocols.

*** INVESTIGATOR'S CHOICE:** Cisplatin or Carboplatin

CALVERT FORMULA FOR CARBOPLATIN DOSING

Total Dose (mg) = (target AUC) x (CrCL by Cockcroft-Gault [Appendix III] + 25)

6.3.2 Cisplatin/Carboplatin and Pemetrexed Dose Modification and Discontinuation Criteria

For any drug-related toxicity/AE that requires dose reduction, chemotherapy should be delayed until recovery and dose modification should be applied as mentioned in Table 7, 8 and 9. These serve as a guide and do not replace investigator judgment and applicable local label recommendations if more stringent.

If chemotherapy needs delay due to drug related toxicity/AE, for those participants on durvalumab withhold **both chemotherapy and durvalumab** until chemotherapy retreatment criteria are met and restart both at the same time. If chemotherapy retreatment is not met or toxicity does not resolve within 3 weeks (before next cycle is due), durvalumab can be continued on schedule provided the retreatment criteria for durvalumab are met.

If chemotherapy retreatment criteria are **met** after three weeks but before six weeks (2 cycles delay) due to drug related toxicity/AE, chemotherapy can be administered when these criteria are met, even if durvalumab has been given at three weeks. Under these circumstances the subsequent durvalumab cycle may be either continued on the planned 3 weekly schedule or delayed to synchronise with subsequent chemotherapy cycles.

If chemotherapy retreatment criteria are **not met** at six weeks (2 cycles delay) due to drug related toxicity/AE, chemotherapy should be permanently discontinued, durvalumab can be continued on schedule provided the retreatment criteria for durvalumab are met.

Table 7: Recommended Dose Modifications/Discontinuation Criteria for Cisplatin, Carboplatin and Pemetrexed Toxicities

	Dose level 0	**Dose Level -1**	**Dose Level -2**	**Dose Level -3**
Cisplatin	75 mg/m^2	60 mg/m^2 or switch to Carboplatin AUC 5 (per investigator choice)	50 mg/m^2 or switch to Carboplatin AUC 5 (per investigator choice)	Discontinue
Carboplatin	AUC 5	AUC 4	AUC 3	Discontinue
Pemetrexed	500 mg/m^2	375 mg/m^2	250 mg/m^2	Discontinue

Table 8: Recommended Dose Modifications for Chemotherapy Hematological Toxicity

		Pemetrexed	**Cisplatin/Carboplatin**
Platelets	**ANC**	**Dose Level (DL from Table 7)**	
≥ 50 AND	≥ 0.5	DL 0	DL 0
≥ 50 AND	< 0.5	DL -1	DL -1
<50 without bleeding AND	ANY	DL -1	DL -1
< 50 with Grade **≥ 2 bleeding and**	ANY	DL -2	DL -2
ANY AND	< 1.0 + fever **≥ 38.5ºC (101ºF)**	DL -1	DL -1

Table 9: Recommended Dose Modifications for Chemotherapy Non-Hematological Toxicity

		Pemetrexed	Cisplatin	Carboplatin
Event	**CTC Grade**	**Dose Level (DL from Table 9)**		
Nausea or vomiting	Grade 3 or 4	DL 0	DL 0	DL 0
Diarrhoea	Grade 3 or 4	DL -1	DL -1	DL -1
Mucositis	Grade 3 or 4	DL -2	DL 0	DL 0
Neurotoxicity	Grade 2	DL 0	DL -2	DL 0
	Grade 3 or 4	DL -1	Discontinue	DL -1
Transaminase elevation	Grade 3	DL -1	DL -1	DL -1
	Grade 4	Discontinue	Discontinue	Discontinue
Other non-hematological toxicity	Grade 3 or 4	DL -1	DL -1	DL -1
Hypersensitivity reaction	Severe	Discontinue	Discontinue	Discontinue

If platinum is discontinued, i.e. no further cisplatin OR carboplatin will be given, then pemetrexed should also be discontinued.

If any of the above events occur, participants can continue therapy with durvalumab if:

- None of the withdrawal criteria for durvalumab have been met
- All drug-related adverse events that occurred during previous cycles have recovered to baseline levels, or to CTCAE grade levels that would allow further durvalumab treatment
- Participants have already received at least one cycle of combination cisplatin/carboplatin and pemetrexed.

If pemetrexed is discontinued, then platinum should also be discontinued, i.e. no further cisplatin or carboplatin should be given.

6.3.3 Retreatment Criteria for Cisplatin/Carboplatin and/or Pemetrexed

Re-treatment criteria for further cisplatin/carboplatin and pemetrexed cycles are as follows:

- ANC ≥ 1.5 x 10^9/L
- Platelet count ≥ 100 x 10^9/L

In addition, the following pre-treatment values have to be reached for cisplatin/carboplatin re-treatment:

- Creatinine clearance (CrCl) ≥ 60 mL/min (≥ 40 mL/min sufficient for carboplatin); use Cockcroft-Gault formula as per Appendix 3 - Cockcroft-Gault formula)
- Total bilirubin ≤ 1.5 x ULN (except participants with Gilbert's Syndrome, who are eligible with bilirubin ≤ 2.5 x ULN)
- Alanine transaminase ≤ 3 x ULN, unless liver metastases or invasion are present, in which case it must be ≤ 5 x ULN
- Aspartate aminotransferase ≤ 3 x ULN, unless liver metastases or invasion are present, in which case it must be ≤ 5 x ULN

6.3.4 Toxicity Management Guidelines for Chemotherapy and Durvalumab Combination

Non-overlapping toxicities are expected for durvalumab and cisplatin/carboplatin and pemetrexed. Dose reductions and modifications should be performed according to the toxicity profiles of each agent and the putative causative agent of the AE as mentioned above.

6.4 *Ipilimumab and Nivolumab*

6.4.1 Ipilimumab and Nivolumab Administration

Ipilimumab:
Ipilimumab 1 mg/kg will be administered IV every 6 weeks in conjunction with nivolumab. Ipilimumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution and is to be administered as a 30 minute IV infusion as outlined in the IB. Ipilimumab must be administered via 0.2 micron or 1.2 micron, low protein binding in-line filter.

Nivolumab:
Nivolumab can be given as a flat dose at 360 mg every 3 weeks or 3 mg/kg every 2 weeks as IV infusion. Nivolumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution and is to be administered as a 30 minute IV infusion according to standard local practice. Nivolumab must be administered via 0.2 micron or 1.2 micron, low protein binding in-line filter.

When ipilimumab and nivolumab are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab and will start after the infusion line has been flushed, filters changed and patient has been observed to ensure no infusion reaction has occurred. The time between infusions is per standard institution protocols.

6.4.2 Dose Modifications for Ipilimumab and Nivolumab

The management of imAEs from ipilimumab and/or nivolumab may involve interruptions of ipilimumab and nivolumab, administration of corticosteroids and/or other supportive measures. The management of infusion-related reaction is summarised in Appendix 5 - Management of Immune-mediated Adverse Events (ImAEs), infusion-related reaction and non-immune related reaction.

If discontinuation criteria were met for ipilimumab but not for nivolumab, treatment with nivolumab may continue. Ipilimumab cannot be continued alone.

6.4.3 Dose Delays Ipilimumab and Nivolumab

Dose delay criteria apply to all drug-related AEs. Treatment delay up to **12 weeks** for nivolumab from last dose and up to **12 weeks** for ipilimumab from the last dose are allowable (any dose delays greater than these will require approval from the medical monitor).

Nivolumab and ipilimumab administration, should be delayed for the following:

- Grade ≥ 2 non-skin, drug-related AE except for fatigue
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for asymptomatic amylase or lipase, AST, ALT, or total bilirubin:
  - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay. It is recommended to consult with the study team for Grade 3 amylase or lipase abnormalities.
  - If a participant has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a participant has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication. Early recognition and prompt intervention are essential for imAEs.

Please refer to Appendix 5 - Management of Immune-mediated Adverse Events (ImAEs), infusion-related reaction and non-immune related reaction.

Participants receiving ipilimumab in combination with nivolumab that have drug-related toxicities that meet the criteria for dose delay, should have **both** drugs (ipilimumab and nivolumab) delayed until retreatment criteria are met.

6.4.4 Criteria to Resume Ipilimumab and Nivolumab

If participants experience grade 3 or higher imAE, ipilimumab or nivolumab should be interrupted until symptoms resolve to grade 1 or less with the following exceptions:

- Grade 2 fatigue
- Grade 2 skin toxicity
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

Rescheduling:

- Nivolumab may be delayed until the next planned ipilimumab dose, if the next ipilimumab dose is scheduled within the next 12 days. This will permit periodic ipilimumab dosing to be synchronized with nivolumab dosing.
- Ipilimumab should be dosed at the specified interval regardless of any delays in intervening nivolumab doses. However, in order to maintain periodic synchronized dosing of ipilimumab and nivolumab, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 3 day window, as long as consecutive nivolumab doses are given at least 12 days apart. Ipilimumab may be delayed beyond the 3 day window if needed to synchronize with the next nivolumab dose.
- If an ipilimumab dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent ipilimumab doses should be rescheduled to maintain the 6 week interval between consecutive ipilimumab doses.
- A dose delay of ipilimumab which results in no ipilimumab dosing for >12 weeks requires ipilimumab discontinuation with the following exception: Dosing delays to manage drug-related adverse events, such as prolonged steroid tapers, are allowed.

If the criteria to resume treatment are met, the patient should restart treatment as soon as possible or at the next scheduled time point per protocol. If treatment is delayed >12 weeks, the patient must be permanently discontinued from ipilimumab and nivolumab therapy, except as specified in Section 6.4.5 below.

6.4.5 Management of Infusion Related Reactions to Ipilimumab or Nivolumab

Please refer to Appendix 5 - Management of Immune-mediated Adverse Events (ImAEs), infusion-related reaction and non-immune related reaction.

6.4.6 Permanent Discontinuation of Ipilimumab or Nivolumab

Combined immunotherapy with ipilimumab and nivolumab should be permanently discontinued for the following reasons:

- Any dosing interruption for immune related adverse events lasting >12 weeks for nivolumab or >12 weeks for ipilimumab (unless approved by the study chair).

- Any Grade 2 drug-related uveitis or blurred vision that does not respond to topical therapy and does not improve to baseline severity within the re-treatment (6 weeks) period OR requires systemic treatment. **Note:** patients receiving prophylactic topical steroid eye drops following the resolution of the uveitis can continue treatment if deemed in their best interest.
- Any Grade 3 non-skin, drug-related AE lasting >7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhoea, colitis, neurologic AE, hypersensitivity reactions, and infusion reactions.
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhoea, colitis, neurologic adverse event, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below:
  - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    - AST or ALT >5 x ULN
    - Total bilirubin >3 x ULN
    - Concurrent AST or ALT >3 x ULN and total bilirubin >2 x ULN
- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to <Grade 4 within 1 week of onset
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - New onset of an endocrinopathy that can be adequately managed with hormones supplements (e.g. type 1 diabetes managed with insulin supplementation)

Note: If nivolumab is discontinued for any reason, ipilimumab should not be continued alone. Treatment with nivolumab may continue if ipilimumab is discontinued.

If a participant meets criteria for discontinuation and the investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and ipilimumab.

A participant being treated with ipilimumab and/or nivolumab and deemed to be clinically benefiting despite initial progression on imaging (e.g. suspected pseudoprogression) may continue ipilimumab and/or nivolumab at the discretion of the treating investigator. In this case, a confirmatory follow-up scan should be performed 4 weeks to 8 weeks later.

6.5 *Post-Study Treatment*

Treatment after discontinuation of study treatment is at the discretion of the patient's clinician.

6.6 *Concomitant Medications*

6.6.1 Recommended for Pemetrexed

Corticosteroid: Skin rash has been reported more frequently with pemetrexed in participants not pre-treated with a corticosteroid. Pre-treatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction. All participants should be pre-medicated with dexamethasone 4 mg by mouth twice daily the day before, the day of, and the day after pemetrexed administration, or as per standard institution protocols.

Vitamin Supplementation: Sites should follow the instructions as per the approved label for pemetrexed/ALIMTA in the US and Australia respectively in order to reduce potential toxicity.

In the United States per reference USPI:

i) Participants must receive vitamin B12, 1 mg intramuscularly, during the week prior to the first dose of pemetrexed/ALIMTA for injection and every 3 cycles thereafter. Subsequent B12 injections may be given on the day of pemetrexed therapy.

ii) Participants must be instructed to initiate folic acid 400 mcg to 1000 mcg orally, once daily, beginning 7 days prior to the first dose of pemetrexed/ALIMTA and continue until 21 days after the last dose of pemetrexed/ALIMTA.

In Australia / New Zealand:

i) To reduce toxicity, participants treated with pemetrexed must be instructed to take a low-dose oral folic acid preparation or multivitamin with folic acid (350 µg to 1000 µg, most commonly used dose of 500 µg) on a daily basis. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of pemetrexed; and dosing should continue during the full course of therapy and for 21 days after the last dose of pemetrexed.

ii) Participants must receive an intramuscular or subcutaneous injection of vitamin B12 (1000 µg) at least one day prior to the first dose of pemetrexed and no more than 4 weeks prior, and once every 9 weeks until pemetrexed is discontinued. Subsequent vitamin B12 injections may be given on the same day as pemetrexed.

6.6.2 Permitted

The following medications and procedures are allowed during this study.

- Best supportive care including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management.
- Palliative radiotherapy to symptomatic areas of disease or urgent local complications which were present at baseline and are not being used for mRECIST measurements is permitted. However, palliative radiotherapy to new lesions or areas of unequivocal tumour progression would be considered as progressive disease.
- Intrapleural instillation of talc for pleural effusion palliation is allowed.
- Inactivated vaccines are allowed on weeks study treatment is not received.
- See Appendix 4 Acceptable Birth Control Methods.

6.6.3 Prohibited

The following medications should not be used during this study. Participants who require treatment with any of these agents will usually need to discontinue study treatment. This should be discussed with the Study Chair by contacting the NHMRC CTC for Australia or PrECOG Operational Team for US sites:

- Other concurrent investigational treatments or anti-cancer therapy, other than cisplatin/carboplatin, pemetrexed and ipilimumab or nivolumab.
- Live attenuated vaccines (including shingles vaccine) cannot be given <30 days before the first dose of durvalumab, ipilimumab or nivolumab, during treatment with durvalumab, ipilimumab or nivolumab and for 30 days post discontinuation of durvalumab, ipilimumab or nivolumab.
- Patients should not donate blood while participating in this study, or for at least 90 days following the last infusion of durvalumab, ipilimumab or nivolumab or 90 days after receipt of the final dose of durvalumab, ipilimumab or nivolumab.
- Herbal and natural remedies which may have immune-modulating effects.

6.6.4 Use with Caution

- Corticosteroids (>10 mg daily prednisone or equivalent dose of an alternative corticosteroid) or other immunosuppressive medications should be avoided unless they are necessary:
  - To treat severe adverse events, e.g. autoimmune phenomena, or brain metastases
  - To facilitate administration of cisplatin/carboplatin and pemetrexed (for up to 5 days)
  - As a temporary measure for other indications at the discretion of the principal investigator (e.g. chronic obstructive pulmonary disease, radiation, nausea, etc.)

6.6.5 Concomitant Medication Reporting

The reporting period for concomitant medications is from randomisation until 30 days after the last dose of chemotherapy or until 90 days after the last dose of durvalumab, ipilimumab or nivolumab, whichever is the latest. Concomitant medications must be recorded in the participant's medical record for each assessment. Concomitant medications administered at time of a serious adverse event must be reported into the eCRF at the time of reporting the serious adverse event.

7 ASSESSMENT PLAN

7.1 *Schedule of Assessments*

Phase **Timing**	**Screening** within 14 days prior to randomisation	**On each day of study treatment administration**[18] window up to 3 days before	**Post-Completion of Treatment**[14] within 4 weeks +/- 7 days	**Post-Treatment Discontinuation until Progression** Q 6-weekly +/- 7 days	**Post-Progression** Q 12-weekly +/- 14 days
History and Physical examination					
Written informed consent[17]	X				
Verify eligibility	X				
Medical history[16]	X				
Vital signs[1]	X	X	X		
Clinical assessment[2]	X	X	X	X	
ECOG Performance Status	X	X	X	X	
Adverse Events		X	X	X[15]	
Concomitant medications	X	X	X	X[15]	
Laboratory Assessments					
Blood for haematology/biochemistry[3]	X	X	X	X[15]	
Thyroid Function Tests[4]	X	X (every 6 weeks)	X	X[15]	
Cortisol level[5]	X	As per local practice and when clinically indicated			
Coagulation tests[6]	X	As per local practice and when clinically indicated			
Hepatitis B and C serology[7]	X				
Radiology					
CT chest with contrast and other sites of known disease[8]	X[8]	Weeks 6, 12, 18, 26, 34, 42, 50, then 12 weekly until disease progression (+/- 7 days)			
Other investigations					
Pregnancy test in WOCBP[9]	X	As per standard of care			
Urinalysis[10]	X	As per standard of care			
Electrocardiogram	X	As per standard of care			
Health Related Quality of Life (HRQL) assessment[11]	X	Weeks 6, 12, 18, 26, 34, 42, 50 and then 12 weekly until disease progression (+/- 7 days) AND at the first post-progression assessment			
Correlative studies					
Blood for translational research[12]		Baseline (prior to first dexamethasone administration), week 2 or week 3 (depending on treatment), week 6 window up to 3 days earlier, except baseline up to 7 days earlier			
Survival and anti-cancer treatments				X	X[13]

Footnotes

1. Participants will have their temperature, blood pressure, pulse rate and respiratory rate recorded as detailed in Section 7.2.1.3.
2. Full physical examination, weight and height before starting treatment however these do not need to be repeated if done within 14 days prior to day 1 of cycle 1. Targeted physical examination at other time points as per standard of care.
3. Haematology tests must include a full blood count and differentials.
   Clinical chemistry tests must include the following: bicarbonate or CO2, urea, creatinine, total bilirubin, albumin, total protein, AST, ALT, GGT (only at baseline and if clinically indicated), ALP, LDH, calcium, magnesium, phosphate, chloride, potassium, sodium, glucose and lipase (or amylase).
   Haematology and clinical chemistry tests do not need to be repeated if done within 14 days prior to day 1 of cycle 1.
   Beyond cycle 1 safety bloods must have been done within 3 days of treatment and be available and reviewed prior to each treatment.
4. After screening sample, obtain on immunotherapy participants only. Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is a clinical suspicion of an adverse event related to the endocrine system.
5. Repeated only if clinically indicated.
6. Coagulation tests, including prothrombin time (PT), activated partial thromboplastin time (APTT) and international normalised ratios (INR) are only mandated at screening; may otherwise be performed if clinically indicated.
7. Hepatitis B (HBV surface antigen [HBsAg]) and hepatitis C (HCV antibody) testing: only if not previously available within the past 12 months. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
8. Baseline CT within 28 days prior to randomisation. After commencement of study treatment, CT every 6 weeks after randomization for the first 18 weeks and then every 8 weeks until week 50 then 12 weekly thereafter until confirmed progressive disease (PD). Imaging data is uploaded for storage in a central repository to allow central review and imaging research to validate response criteria. If iUPD occurs, confirmatory scans must be performed at least 4 weeks, but no longer than 8 weeks, after iUPD was identified. Treatment efficacy (RECIST) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of randomisation (not the date of therapy).
9. Serum BHCG for women of child-bearing potential (WOCBP) must be tested.
10. Urinalysis is performed at screening and as clinically indicated. A dipstick urinalysis will be performed routinely and include an assessment of bilirubin, blood, glucose, ketones, pH, protein, specific gravity, colour and appearance. Additional microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.
11. HRQL (EORTC QLQ C30 and LC29 [plus EQ-5D-5L for Australian sites only]) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of randomisation (not the date of therapy). HRQL assessments should be completed before imaging results are discussed with the patient wherever possible. HRQL assessments should be completed on the assessment at which progression is identified and on first post-progression assessment.
12. Please note baseline research blood sample **MUST** be collected prior to pre-chemotherapy dexamethasone.
    Experimental group: Chemotherapy and durvalumab or Control group: Chemotherapy (1 cycle = 3 weeks)
    Baseline (prior to start of dexamethasone Cycle 1 Day 1)
    a. Cycle 2 Day 1
    b. Cycle 3 Day 1

    Control group: Ipilimumab and nivolumab (1 cycle= 6 weeks)
    a. Baseline (Cycle 1 Day 1)
    b. C1D15 (if on 2-weekly nivolumab) or C1D22 (if on 3-weekly nivolumab)
    c. Cycle 2 Day 1

13. Contact by phone is acceptable.
14. This visit is to be performed 7-8 weeks after the last dose of study treatment +/- another 7 days.
    For Experimental Group this refers to maintenance treatment with durvalumab.
    For Control Group this refers to chemotherapy or immunotherapy (platinum-chemotherapy and pemetrexed or ipilimumab and nivolumab).
15. Until **30 days** after last dose of chemotherapy, and **90 days** after last dose of durvalumab, ipilimumab or nivolumab, whichever is the latest.
16. Including smoking history and asbestos exposure.
17. Consent within 28 days of randomisation.
18. Treatment window is +/- 3 day.

7.2 *Details of Assessments*

Before study entry, throughout the study, and following study drug discontinuation, clinical and diagnostic laboratory evaluations are outlined to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedule of Study Assessments during the screening and treatment period is provided in Section 7.1 Schedule of Assessments.

7.2.1 Clinical Assessment

7.2.1.1 Physical Examination

A full physical examination will be performed at screening and will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck, lymph nodes, thyroid, musculoskeletal, and neurological systems and at screening only, height. A targeted physical examination as clinically indicated will be performed on subsequent evaluations.

7.2.1.2 Electrocardiogram

ECGs are required during screening, as well as at any other time point when clinically indicated.
All 12-lead ECGs should be recorded while the participant is in a supine position, resting for at least 5 minutes in each case. At Screening, a single ECG will be obtained on which QTcF must be <470 ms. In case of clinically significant ECG abnormalities, including a QTcF value ≥ 470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.

Calculator:
https://www.thecalculator.co/health/QTc-Calculator-385.html

If additional ECGs are required the same method of assessment should be used throughout the study.

7.2.1.3 Vital Signs

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured before, during and after the immunotherapy (durvalumab, nivolumab, ipilimumab) infusion. These values will be recorded in the medical record.

On the first immunotherapy (durvalumab, nivolumab, ipilimumab) treatment day, vital signs will be measured at the following times:

First infusion

- prior to the beginning of the infusion of immunotherapy (durvalumab, nivolumab, ipilimumab) (measured once from approximately 30 minutes before up to 0 minutes [i.e. the beginning of the infusion])
- 30 minutes during the infusion (± 10 minutes)
- at the end of infusion (+ 5 minutes)
- If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles as described above or more frequently if clinically indicated, including when the infusion rate is slowed or temporarily stopped as per Section 6.2.3 for durvalumab and Appendix 5 for ipilimumab and nivolumab.
- In the one hour observation period post-infusion: 30 and 60 minutes after infusion (i.e. 90 and 120 minutes from the start of the infusion) +/- 15 minutes – for the FIRST infusion only and then for subsequent infusions only if clinically indicated.

Subsequent infusions

BP, pulse and other vital signs should be measured prior to the start of the infusion. Patients should be carefully monitored and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated.

7.2.2 Imaging

Contrast enhanced CT chest and any site of known disease is required for this study. CT scans and study tumour assessments should be performed per mesothelioma imaging guidelines as noted in the Radiology Manual. Low dose CT imaging is not acceptable. Non contrast enhanced CT of chest and any site of known disease can only be utilized if contrast is contraindicated for the patient.
Tumour measurements on worksheets and in the database should be rounded to the nearest mm and should not be recorded in decimal places e.g. 5.8 mm would be recorded as 6 mm.

7.2.3 Health Related Quality of Life (HRQL)

7.2.3.1 EORTC QLQ C30 and LC29 Questionnaires

The assessment of Quality of Life (QoL) in all participants is an important aspect in this trial. The addition of an immune based therapies to standard platinum based chemotherapy may have positive (if increased activity) or negative effects (if increased toxicity) on participant well-being. Potential survival gains from new therapy in combination with standard therapy need to be assessed in terms of their QoL impact as incremental toxicity, especially immune mediated toxicities such as colitis, pneumonitis, endocrinopathies or pseudoprogression may adversely impact participant well-being. Thus, a participant perspective of the impact of treatment is an essential part of this study.
Participants will complete Health Related Quality of Life (HRQL) questionnaires EORTC QLQ C30 and LC29 every 6 weeks for the first 18 weeks and then every 8 weeks until week 50 then 12 weekly thereafter until confirmed progressive disease. HRQL assessments should be completed before imaging results are discussed with the participant wherever possible. HRQL assessments should be completed on the assessment at which progression is identified and on first post-progression assessment.
Questionnaires will be provided in English, either as a hardcopy for completion at the clinic visit, or electronically using participant/site device using ePRO software.
Site staff should explain to participants that:

- Responses are confidential and will not impact their care, therefore participants should raise any concerns with their doctor.
- HRQL assessments are important so the research team can learn about how the treatment impacts quality of life, their daily functioning and disease symptoms.
- The questionnaire lists some issues that they may or may not be experiencing. Each question has four response options: “not at all, a little, quite a bit, very much”. Participants should please answer all of the questions themselves by selecting the number that best applies to them. There are no “right” or “wrong” answers.
- The information provided will be very useful for future patients, and will help them understand what to expect from this treatment.

The EORTC core QoL questionnaire (QLQ-C30) (46) and lung cancer module (QLQ-LC29) (47) will be used in this trial. The QLQ-C30 is well-validated and has been adapted for multiple languages, which is essential for this multinational study . The EORTC QLQ-C30 and QLQ-LC29 include items that address the main side effects of chemotherapy as well as immunotherapy. The QLQ-LC29 is the recently updated version of the QLQ-LC13 questionnaire. The revised version includes side-effects relevant to targeted therapies, in addition to 12 of the 13 items from the QLQ-LC13. The QLQ-LC29 has been validated in small cell and non-small cell lung cancer.
The EORTC QLQ-C30 (46) is a self-administered cancer specific questionnaire with multi-dimensional scales. It consists of both multi-item scales and single item measures, including five functioning domains, a global quality of life domain, three symptom domains and six single items.
The QLQ-LC29 lung cancer module (48) includes questions assessing lung cancer associated symptoms (cough, hemoptysis, dyspnea, and site-specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia, items address dry/itchy skin, allergic reactions, dizziness, burning eyes, problems speaking, weight loss, thin/lifeless hair, and 5 surgical items (if applicable) The EORTC QLQ-C30 and module will be scored according to the EORTC QLQ-C30 Scoring Manual, and analyzed accordingly. For each domain or single item measure a linear transformation will be applied to standardize the raw score to range between 0 and 100.

7.2.3.2 EQ-5D-5L Questionnaire

The EQ-5D self-administered questionnaire consists of two pages comprising the EQ-5D-5L descriptive system and the EQ Visual Analogue Scale (VAS). The EQ-5D-5L descriptive system comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and each dimension comprises five levels (no problems, slight problems, moderate problems, several problems and extreme problems). A unique EQ-5D-5L health state is defined by combining one level from each of the five dimensions. The VAS records the respondent's self-rated health status on a vertical graduated (0-100) visual analogue scale. The EQ-5D-5L is a validated instrument that has been used in population surveys and clinical trial settings. Analysis will be performed as detailed in the health economics section of the protocol.

US sites also please refer to Appendix 10: Ethics and Regulatory Compliance for USA Sites.

7.2.4 Healthcare Resources

Australian Sites:

A prospective economic evaluation will be conducted in all participating centres in Australia to determine the incremental cost-effectiveness and cost-utility of adding standard platinum combination chemotherapy to immunotherapy in advanced pleural mesothelioma from a government payer perspective, by prospectively collecting economic and resource utilization information during the trial.

Information on the following areas of healthcare resource use will be collected: hospitalisations (for all participants by trial staff via a standard CRF), visits to health professionals [for Australian participants via Medical Benefits Schedule (MBS)], and prescribed medications [for Australian participants via Pharmaceutical Benefits Scheme (PBS)]. Approval will be obtained to collect this information. Consent will be sought from Australian participants for access to their MBS and PBS records. The mean per patient volume of healthcare use and costs as well as total healthcare costs will be tabulated for experimental and control groups of the trial at 24 months. Healthcare use will be valued using the most recent reference pricing (i.e. DRG cost weights) for inpatient admissions, and unit costs for MBS and PBS items.

7.2.5 Blood Collection

Local pathology laboratories will be used for routine blood tests. Blood will be taken prior to the administration of each cycle.

Central laboratories will be used to evaluate circulating biomarkers.

Blood will be collected and initially processed and stored at each study site. Some research blood may also be collected and shipped to central laboratories for processing in real-time for translational research studies. At selected sites, blood will also be collected to recover peripheral blood mononuclear cells (PBMCs) from all participants at those sites. Refer to Biospecimen Sampling Manual for procedures.

Translational research blood collection time points are as follows:

Experimental group: Chemotherapy and durvalumab or Control group: Chemotherapy (1 cycle = 3 weeks)

- Baseline (prior to start of dexamethasone Cycle 1 Day 1)
- Cycle 2 Day 1
- Cycle 3 Day 1

Control group: Ipilimumab and nivolumab (1 cycle= 6 weeks)

- Baseline (Cycle 1 Day 1)
- C1D15 (if on 2-weekly nivolumab) or C1D22 (if on 3-weekly nivolumab)
- Cycle 2 Day 1

Refer to Biospecimen Sampling Manual for further details

US sites also please refer to Appendix 10: Ethics and Regulatory Compliance for USA Sites

7.2.6 Tissue Collection

Paraffin-embedded tissue will be collected for central histology (mandatory for eligibility), and translational research. Where archival tumour tissues are available from more than one occasion, the latest obtained

sample should preferentially be retrieved for translational research whenever possible if appropriate for the research purpose. Additional consent (optional) will be sought for use of tissue (including if a biopsy is clinically indicated during or after treatment) for translational research. Refer to the Biospecimen Sampling Manual for procedures.

US sites also please refer to Appendix 10: Ethics and Regulatory Compliance for USA Sites

7.3 *Follow-Up after Treatment*

Participants will be followed up to 30 days after last dose of chemotherapy or 90 days after last dose of immunotherapy as described in Section 8.2.
All participants, including those who discontinue protocol therapy early, will continue to have tumour assessment until progression, and for survival via phone/clinic visit/registry review until study closure.

8 OUTCOMES, ENDPOINTS AND OTHER MEASUREMENTS

8.1 *Overall Survival (OS)*

OS is the primary endpoint of this study. It is defined as the time from randomisation to the date of death due to any cause. Participants who are alive at the time of the final analysis or who have become lost to follow-up will be censored at their last known alive date.

8.2 *Progression Free Survival (PFS)*

PFS is defined as the interval from date of randomisation to the date of first evidence of disease progression or death, whichever occurs first. The date of first disease progression based on imaging is that of the first positive scan, even if this is determined in retrospect, based on modified RECIST 1.1 for PM and iRECIST (Section 17.1 and 17.7). Results for PFS based on iRECIST will be considered exploratory. If a participant commences non-protocol anti-cancer therapy prior to documented imaging progression they will be considered to have progressed on that date.

8.3 *Objective Tumour Response Rate (OTRR)*

The objective tumour response rate is defined as the proportion (percentage) of participants with a confirmed response of either CR or PR assessed by the investigator according to modified RECIST 1.1 criteria for assessment of response in pleural mesothelioma (Appendix 1 – Section 17.1) and according to iRECIST (Section 17.1 and 17.7) based on evaluable response assessments performed up until progression or commencement of non-protocol anti-cancer therapy, whichever occurs first. Results for OTRR based on iRECIST will be considered exploratory.
A confirmed response is defined as a response (CR or PR) followed by confirmation of response (CR or PR) at a subsequent assessment at least 4 weeks after the first observation of response.

8.4 *Adverse Events*

The NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 will be used to classify and grade the intensity of adverse events (refer to Section 17.6, Appendix 6).

8.5 *Health-Related Quality of Life (HRQL, EORTC QLQ-C30, QLQ-LC29, EQ-5D-5L)*

The HRQL tools will be evaluated and scored according to their respective scoring manuals. This will in turn provide an overall score for each tool in order to determine the effects treatment has on participants QoL.
The EORTC-recommended scoring guidelines will be used. A raw score was calculated as the average of items contributing to a scale. A linear transformation was used to standardize the raw scores to a 0- to 100-point range. A ≥ 10-point score change within a participant in any scale (e.g., symptoms, function, global health status) will be considered to be the threshold of a clinically meaningful change (49). An increase in the score for the global health status and functioning scales will be indicative of improvement, and a decrease in the score for the symptom scales or items was indicative of a reduction in symptom severity.
Changes of the quality of life scores while on treatment versus baseline will be examined using analysis and descriptive statistics. Specific time points will be checked to explore treatment side effect on participants QoL, and the long term benefit of the study treatment. In addition, baseline scores will be compared using a Wilcoxon rank sum test, and a pattern mixture model identifying drop-out participants as a special category, will be performed to evaluate the effect of missing data. Time to deterioration in QOL will be analysed.

As part of the economic evaluation in this study, quality of life weights, (utilities), will be measured using the EQ-5D-5L questionnaire, using data from randomised Australian participants. Assessment time points will enable evaluation of the impact on QALY weights (i.e. utilities) of chemotherapies and immunotherapies for durvalumab in the experimental group, and ipilimumab and nivolumab in the control group. Data will be explored for informative censoring, and relevant imputation methods may be undertaken. Australian value sets will be used for the utility calculation. The distribution of EQ-5D-5L values will be plotted, and means with precision estimates for the experimental and control groups will be tabulated. Clustering of EQ-5D-5L values will be explored (50). Quality-adjusted survival, (QAS) at 24 months will be calculated by applying utility weights derived from the EQ-5D-5L instrument to survival data using established methods.
Additional analyses will be conducted using NHMRC CTC standard analysis programs.
Pre-specified PRO outcomes are detailed in the statistical analysis plan and where relevant, the health economics analysis plan (HEAP).

8.6 *Healthcare Resource Use*

A within trial economic evaluation will determine the incremental cost-effectiveness and cost-utility of durvalumab in addition to chemotherapy for participants enrolled in Australia. The perspective will be of the government health system. Hospitalisations, outpatient visits, diagnostics and medicines including chemotherapies and immunotherapies in experimental and control groups will be identified, measured and valued.
Australian unit costs will be applied to the healthcare use data (e.g. Australian Refined Diagnostic Related Groups (AR DRG) costs for hospitalisations, and scheduled costs for Medical Benefits Schedule (MBS) and Pharmaceutical Benefits Schedule (PBS) items) to estimate the mean per patient and total healthcare costs for the experimental and control groups. Differences in overall mean costs between randomised groups will be presented using means and 95% confidence intervals. Cost data will be subsequently analysed using Generalised Linear Models. The distribution of residuals from the regression model will be examined and a decision will be made as to whether the costs should be logarithm transformed. Further regression models will adjust for baseline covariates (such as age, sex, state) known to influence resource utilisation.

8.7 *Incremental Cost Effectiveness*

A within-trial economic evaluation will determine the incremental cost-effectiveness and cost-utility of durvalumab in addition to chemotherapy or ipilimumab and nivolumab at 24 months, for participants enrolled in Australia, from a health system perspective. Outcomes of interest will include: mean per patient costs, life years (LY) gained, and quality adjusted life years (QALY) gained between comparators. From this data, an incremental cost/LY (Dollars/LY) gained and cost/QALY (Dollars/QALY) gained ratio will be calculated.
The most recent Australian unit costs will be applied to the resource usage data (e.g. Australian Refined Diagnostic Related Groups (AR DRG) costs for hospitalisations, and scheduled costs for Medical Benefits Schedule (MBS) and Pharmaceutical Benefits Schedule (PBS) items) to estimate the incremental cost of the addition of durvalumab to standard treatment.
Quality-adjusted survival (QAS) time will be used to quantify the incremental effectiveness of the new treatment regimen. QAS will be calculated by applying utility weights for quality of life derived from the EQ-5D-5L 'utility instrument' to survival data using established methods. Costs and health outcomes will be discounted in the second year by 5%. A cost-effectiveness acceptability curve (CEAC) will be constructed showing the probability of the intervention being cost-effective at different Government willingness to pay thresholds.
Uncertainty in the cost-effectiveness results will be assessed through a series of sensitivity analyses, varying the important costs and outcomes such as the cost of durvalumab, ipilimumab and nivolumab, progression free survival, and utilities for different health states. Sub-group analyses will be undertaken to explore cost-effectiveness by the pre-determined strata: Age (18-70 years vs older than 70); Sex (male vs female); platinum chemotherapy (cisplatin or carboplatin) and planned control regimen (chemotherapy or ipilimumab and nivolumab). Further details will be documented in the health economics analysis plan (HEAP).
Completion of this evaluation of health related quality of life and costs of combining chemotherapy regimens with durvalumab and use of ipilimumab and nivolumab in this randomised trial will inform health policy, practice and future treatment regimens for mesothelioma patients. The adoption and governmental/third party payer funding of new cancer therapeutics is dependent on the demonstration of cost effectiveness. Therefore, accurate prospective economic data for any new therapeutic is critical to assist decision makers regarding

funding issues. Economic evaluation in other regions will be undertaken at the discretion of the regional groups/coordinating centres.

8.8 *Tertiary/Correlative Measures*

Translational research studies aim to identify biomarkers that may be prognostic and/or predictive of response to treatment, safety and resistance to treatment (associations of biomarkers with clinical outcomes). We aim to identify biomarkers that are predictive of response to therapy with cisplatin/carboplatin, pemetrexed and durvalumab based on biological samples from either before treatment or very early in the course of treatment. We will therefore collect blood samples for research at 3 time points: baseline (prior to start of dexamethasone), Cycle 2 Day 1 and Cycle 3 Day 1. Samples will be collected and stored as per the Biospecimen Sampling Manual. The primary and secondary endpoints for the trial will be determined before the samples are assessed for biomarkers. Biospecimens will be shipped centrally for analyses.
Studies may include, but are not limited to investigating:

- STAT expression and activation in pre-treatment tumour;
- Leucocyte sub-sets and activation/proliferation, including Treg and myeloid-deprived suppressor cells, and gene expression profiles;
- PD-L1 expression in peripheral blood and pre-treatment biopsies;
- The effect of treatment on the T cell repertoire in peripheral blood before and early during treatment;
- Soluble factors (including growth factors and cytokines) in peripheral blood;
- Analysing tumour gene expression signatures;
- Nucleic acid studies (DNA-based, RNA-based) – such as ctDNA studies, tumour mutational burden and genomic DNA/RNA sequencing and functional immunologic assays in selected participants;
- Cellular and molecular signatures associated with imAEs.

Since the identification of new biomarkers correlating with disease activity and the efficacy or safety of treatment are rapidly evolving, the definitive list of biomarkers remains to be determined.

9 SAFETY REPORTING

9.1 *Definitions*

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product (see below).
AEs include the following:

- All suspected adverse drug or device reactions
- All reactions from drug or device – overdose, abuse, withdrawal, sensitivity, toxicity or failure of expected pharmacological action (if appropriate)
- Apparently unrelated illnesses
- Worsening (severity, frequency) of pre-existing illnesses or symptoms
- Injury or accidents
- Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test). Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug or device.

A SERIOUS ADVERSE EVENT (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (i.e. the participant is at risk of death at the time of the event),
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,

- other important medical events which, in the opinion of the investigator, are likely to become serious if untreated, or as defined in the protocol

NOTES:

(i) The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

(ii) Important medical events which may not be immediately life-threatening or result in death or hospitalization but which may jeopardize the patient or may require intervention to prevent one of the listed outcomes in the definition above should also be considered serious.

(iii) For the purposes of this study, the development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the participant's inclusion in this study.

In Australia the following definitions are used for reporting of safety events;

- A SIGNIFICANT SAFETY ISSUE (SSI) is defined as is a safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. These events may be in addition to the current SAE/SADR/SUSAR reports and generally have a consequence related to patient safety within the current study protocol, which thus requires some type of amendment.
- An URGENT SAFETY MEASURE (USM) is one type of significant safety issue where sponsors or trial investigators act immediately to protect participants from an immediate hazard to their health and safety. USMs are often instigated before the TGA and HREC are notified. In these cases, it is strongly recommended that the sponsor contact the TGA within 24 hours of the measure being taken. Examples include:
    - a serious adverse event that could be associated with the trial procedures and that requires modification of the conduct of the trial
    - a hazard to the patient population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease
    - a major safety finding from a newly completed animal study (such as carcinogenicity)
    - a temporary halt/termination of a trial for safety reasons
    - recommendations of the Data Safety Monitoring Board, where relevant for the safety of participants, such as an increase in frequency or severity of an expected adverse reaction
    - single case events (e.g. toxic epidermal necrolysis, agranulocytosis, hepatic failure) that lead to an urgent safety measure)

SSIs or USMs do not necessarily meet all criteria to be considered an SAE. For purpose of safety reporting, these events are to be reported as SAE with a note that this concerns an SSI or USM.

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that is related to the drug or device and is unexpected, i.e. not listed in the investigator brochure or approved Product Information; or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the Participant Information Sheet and Informed Consent Form or elsewhere in the protocol. An event is causally related if there is a reasonable possibility that the drug [intervention] caused the AE, i.e. there is evidence to suggest a causal relationship between the drug and the event.

For the purposes of this study, the following adverse events are not reported to the responsible coordinating centre as SAEs:

- Hospitalisations related to management of the disease under study
- Deaths related to disease under study
- Elective hospitalisations to facilitate the administration of treatment, e.g. Porta-Cath insertion
- Elective hospitalisations for other procedures, e.g. screening colonoscopy, stent change, cardiac catheter, etc.

An ADVERSE EVENT OF SPECIAL INTEREST (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or non-serious. If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the regional coordinating centre.

AESIs observed with immunotherapy (durvalumab, nivolumab, ipilimumab) include:

- Diarrhoea / Colitis and intestinal perforation
- Pneumonitis / ILD
- Hepatitis / transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis (including pemphigoid)
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase or amylase increases
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g. non-infectious meningitis, non-infectious encephalitis, autonomic neuropathy, Guillain-Barré, and myasthenia gravis)
- Myocarditis
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological and rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.
Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochure or product information for ipilimumab and nivolumab. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Appendix 5 – Section 17.5). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

9.2 *Recording Adverse Events*

AEs will be recorded from randomisation until 30 days after the last dose of chemotherapy or until 90 days after the last dose of durvalumab, ipilimumab or nivolumab, whichever is longer. The National Cancer Institute Common Terminology Criteria for Adverse Events version 5 (NCI CTCAE v5.0) will be used to classify and grade the intensity of AEs after each treatment cycle. The worst grade will be recorded for each event.
The following information will be recorded for each SAE**:**

- Event description including classification according to NCI CTCAE
- Reason for classification as an SAE (death, hospitalisation etc.)
- Severity / worst grade
- Attribution to study intervention
- Expectedness (listed in IB/product information for durvalumab, ipilimumab, nivolumab or cisplatin/carboplatin and pemetrexed)
- Action taken with study intervention including rechallenge (if done)
- Outcome of SAE, including end date if recovered.

9.3 *Pregnancy*

In the event of a pregnancy occurring during the course of a study, the participant must be withdrawn from study drug immediately. Pregnancies occurring up to 6 months after the completion of the study drug must also be reported to the investigator. The investigator should counsel the participant; discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

If the partner of a participant becomes pregnant while the participant is on treatment, then the investigator should counsel the participant; discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

9.3.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, the study drug should be discontinued immediately.
Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the participant was discontinued from the study.
If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform their coordinating centre within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.
The relevant regional coordinating centre will work with the Investigator to ensure that all relevant information is provided within 1 to 5 calendar days. The appropriate regional coordinating centre will report to NHMRC CTC using the designated safety reporting e-mailbox within 7 calendar days or sooner when required, for pregnancies with SAEs and within 30 days for all other pregnancies.
The same timelines apply when outcome information is available.

9.3.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of chemotherapy or 90 days after the last dose of immunotherapy, whichever is the longer time period.
Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 6 months after the last dose of chemotherapy or 90 days after the last dose of immunotherapy, whichever is the longer time period should, if possible, be followed up and documented.
Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the participant's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

9.4 *Reporting of Serious Adverse Events (including SUSARs, SSIs and USMs)*

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is from randomisation until 30 days after the last dose of chemotherapy or until 90 days after the last dose of durvalumab, ipilimumab or nivolumab, whichever is longer.

The investigator is responsible for reporting all SAEs (including SUSARs), SSIs and USMs occurring during the study to the NHMRC CTC within 24 hours of investigational site staff becoming aware of the event according to the procedure documented in the Study Manual.

The NHMRC CTC will be responsible for providing reports to the Lead Human Research Ethics Committee (HREC) in Australia. The NHMRC CTC will provide SUSAR, SSI and USM reports and SAE line listings to Investigators for submission to local HRECs as required. The investigator must notify the local HREC as required.
PrECOG will provide SUSARs, SAE line listings and other relevant safety reports to Investigators in the USA for submission to local IRBs as required. The investigator must notify the local IRBs as required.
The NHMRC CTC will submit 'reportable safety events' to the TGA in Australia and PrECOG will submit 'reportable safety events' to local regulatory authorities in the USA. Both NHMRC CTC and PrECOG will

submit to the lead site/coordinating centre in other regions, in time to comply with the requisite specified regulatory time windows (usually 7 days for fatal/life threatening events with an 8 day follow-up report, and 15 days for other events). The lead site/centre will be responsible for reporting to the regulatory authorities and Lead Ethics Committees in other participating countries for which they are responsible.

US sites also please refer to Appendix 10: Ethics and Regulatory Compliance for USA Sites.

10 CENTRAL REVIEW

10.1 *Imaging*

Centralised collection of all radiology scans is required for all randomised participants. Radiology reports and images for tumour assessments will be uploaded to the study database. Please refer to the Radiology Manual and eCRF completion guidelines for details. CT images for tumour assessments should be retained at each site. Central review of radiology reports, blinded to randomly assigned treatment group, will be used to corroborate site-investigators' assessments of tumour response and progression. Central review of radiology images to corroborate tumour response and progression is not currently planned.

11 CENTRAL STORAGE OF BIOSPECIMENS

11.1 *Central Tissue Collection*

Formalin-fixed paraffin-embedded (FFPE) tissue blocks or slides of tumour tissue will be collected for translational research from all participants. Tissue will be collected at site and sent to the central tissue laboratories in Australia and the USA for central review (required of all participants) and translational studies (tertiary/correlative objectives) on these biospecimens and storage.
Refer to the respective Biospecimen Sampling Manual for the details regarding central tissue collection.

11.2 *Central Blood Collection*

Central laboratories will be used to conduct translational studies including biomarker analyses. Blood will be collected and initially processed and stored at each site. Samples will later be shipped to central facilities in Australia and the USA for translational research and storage. Some research blood may also be collected and shipped to central laboratories for processing in real-time for translational research studies. Refer to the Biospecimen Sampling Manual for procedures.

12 STUDY TREATMENT SUPPLY AND ACCOUNTABILITY

Refer to Pharmacy Manual for clinical supply management.

12.1 *Durvalumab*

12.1.1 Formulation/Packaging/Storage

Durvalumab will be supplied by AstraZeneca to the International Sponsor, and NHMRC CTC will supply to study sites. Durvalumab will be supplied as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and 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.

12.1.2 In Use Storage and Stability

Total in-use storage time from needle puncture of durvalumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8°C (36-46°F). Durvalumab does not contain preservatives and any unused portion must be discarded.

12.2 *Cisplatin/Carboplatin and Pemetrexed or Ipilimumab and Nivolumab*

12.2.1 Formulation/Packaging/Storage

Chemotherapy or ipilimumab and nivolumab will not be supplied. Cisplatin/carboplatin and pemetrexed or ipilimumab and nivolumab are supplied as the commercial presentation at study sites and must be stored in the original package according to the manufacturers' storage instructions.

12.3 *Supply*

AstraZeneca will supply durvalumab to the International Sponsor free of charge. Sites are to organise their own cisplatin, carboplatin and pemetrexed or ipilimumab and nivolumab supplies, according to institutional standard practice.

12.4 *Drug Accountability*

Durvalumab will be stored in a secure location. Only authorized pharmacy and study staff will have access to this agent. Drug accountability will be reviewed by NHMRC CTC and PrECOG during monitoring visits. .The pharmacy Department at participating institutions will maintain records of all durvalumab received, dispensed for each participant, and destroyed.

The initial supply of durvalumab will be sent directly to the site upon site activation. As needed, additional supplies may be requested by the Principal Investigator (or their authorized designees) at each participating institution. The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return/destruction (site's drug destruction policy must be reviewed and approved by PrECOG or NHMRC CTC before any study drug can be destroyed at a site).

Disposition of cisplatin/carboplatin and pemetrexed or ipilimumab and nivolumab will be carried out as per usual pharmacy practice.

12.5 *Background Treatment*

Standard of care chemotherapy cisplatin/carboplatin and pemetrexed or ipilimumab and nivolumab will be used according to usual hospital practice.

13 STATISTICAL CONSIDERATIONS

13.1 *Sample Size*

The study was planned to enrol a total of 480 participants. The initial randomisation ratio of 2:1 (experimental: control) was changed to 1:1 in protocol version 4. This was expected to result in approximately 260 participants in the experimental group and 220 in the control group, accrued over 33 months, with follow-up for at least an additional 18 months. This would have provided >85% power assuming a median survival of 18 months in the control group and a median survival of 25.7 months in the durvalumab group (target hazard ratio of 0.70). The assumed survival increased in protocol version 4 was due to the transition to pure epithelioid disease. There was an allowance of approximately 8% for lost to follow-up and/or missing data. A single interim analysis was to be conducted according to the Lan-DeMets alpha spending approach using an O'Brien-Fleming stopping boundary.

Recruitment was closed (31/NOV/2023) with 214 participants (131 experimental group, 83 control group). With the smaller than planned sample size, the alternate hypothesis (difference) will be tested against the null hypothesis (no difference) with a 2-sided alpha of 0.05 within the chemotherapy control treatment estimate (Section 13.2, and with 174 participants has 80% power to detect HR<0.59. The effect in the overall cohort, including 214 participants, will be evaluated as a secondary analysis (80% power at HR<0.61). The interim analysis will be conducted with a data close out 9 months after the completion of recruitment with alpha=0.001. The final analysis will be conducted with a data close out 18 months after the completion of recruitment with alpha=0.049.

13.2 *Statistical Analysis*

The primary analysis population will include all chemotherapy control participants (chemotherapy +/- durvalumab). All randomised participants will be included in the secondary analysis. A third analysis will compare the 40 immunotherapy control participants (durvalumab + chemotherapy versus ipilimumab + nivolumab). With the exception of safety data, all analyses will be conducted on an intention to treat basis

(safety analysis will be reported by treatment as received within all participants who received any study treatment). 95% confidence intervals (CI) will be reported for all relevant estimates. A statistical analysis plan will be prepared prior to the final analysis. This document will contain additional detail on the methods described here.

The primary endpoint of the study is overall survival, defined as the time from randomisation to the date of death due to any cause. Participants who are alive at the time of the final analysis or who have become lost to follow-up will be censored at their last known alive date. All randomised participants will be included in the analysis of OS. Kaplan-Meier estimates will be computed for both groups. CI for the median survival will be computed by the method of Brookmeyer and Crowley. In the primary analysis, the two treatment groups will be compared using the log-rank test stratified by stratification factors and protocol version. Cox regression modelling will be used to estimate the treatment effect both on an unadjusted basis and adjusted for stratification variables and protocol version.

Progression free survival (PFS) is a secondary endpoint of this study, defined as the time from randomization to the date of the first documented disease progression (based on mRECIST and iRECIST) or death due to any cause. A participant who stops treatment with study drug and goes on to receive alternative therapy for PM, prior to documentation of disease progression, will be considered to have progressed on that date. A sensitivity analysis will censor for events on the date alternative therapy began. If a participant has not progressed or received alternative therapy, PFS will be censored on the date of the last disease assessment. All randomized participants will be included in the analysis of PFS. All analyses for OS will be similarly performed for PFS.

OTRR will be conducted as per OS analysis plan. Objective tumour response rate (OTRR) is defined as the proportion of participants with a documented complete response, partial response (CR + PR) based on iRECIST criteria. Results for tumor-related endpoints (PFS and ORR) based on iRECIST will be considered exploratory. The primary estimate of ORR will be based on all participants randomized, and compared using Cochran-Mantel-Haeszel test stratified by stratification factors. Quality of life analysis will be conducted per Section 8.5 and/or with appropriate methods to account for repeated measures.

Planned subgroup analyses for the primary and secondary endpoints will be conducted for key groups (stratification factors, pre/post amendment 4) as specified in the analysis plan.

An exploratory analysis of biomarkers will be conducted. These exploratory analyses will be descriptive/graphical in nature, and are designed to generate new hypotheses to be tested in future clinical studies. When parameters of immune response are measured, continuous variables will be summarized with means and standard deviations. Dichotomous and categorical variables will be summarized using proportions with exact 95% confidence intervals and counts, respectively. These summaries will be computed for each treated participant at multiple time points before and after treatment administration as indicated in the study schema. Plots will be used to show changes in immune response parameters. Comparisons in the pre and post-durvalumab responses for each participant will be compared using paired t-tests (or Wilcoxon signed rank tests if appropriate) for continuous variables and McNemar's test for dichotomous or categorical variables. Associations between immune responses will be explored graphically (e.g. scatterplots, boxplots) and numerically (e.g. correlations, $\chi 2$ tests).

13.3 *Interim Analyses*

Interim analyses on OS are planned as per Section 13.1. If the interim analysis is significant, the trial will continue to complete follow-up to enable reliable estimates of survival. Interim results will be reviewed by the study Independent Safety and Data Monitoring Committee (ISDMC) (Section 14.3) who will also monitor selected safety endpoints, accrual and event rates.

14 STUDY ORGANISATION and COMMITTEES

14.1 *Study Coordination*

The study is an investigator-initiated, conducted as an equal collaboration between TOGA (in collaboration with the NHMRC CTC and University of Sydney) and PrECOG, a non-profit research company that focuses on cancer clinical trials. PrECOG, as the study Sponsor in the US, will identify and approve US sites and oversee US site activities. The University of Sydney will be the Sponsor in Australia. This international study will be conducted at a number of regional coordinating centres, each responsible for their own ethics and

regulatory approvals, regional monitoring, medical oversight and facilitation of data collection and query resolution.
Overall study coordination data acquisition and management and statistical analysis will be performed by the NHMRC CTC.
US sites also please refer to Appendix 10: Ethics and Regulatory Compliance for USA Sites.

14.2 *International Trial Steering Committee*

The International Trial Steering Committee (ITSC) will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees).
The ITSC will consider recommendations from the ISDMC about whether to continue the study as planned, modify, or stop it, based on safety monitoring or other information.
Each regional trial coordinating centre will constitute its own regional TMC, including a clinical lead and coordinating centre lead who will represent the region on the ITSC.

14.3 *Independent Safety and Data Monitoring Committee (ISDMC)*

This open label, phase 3 trial has an ISDMC. There will be safety monitoring by the ISDMC approximately every 6 months. The responsibilities of the ISDMC are to advise the TMC on all matters related to the safety of subjects enrolled in the trial, and on selected matters related to the integrity and potential conclusions of study data and the appropriateness of continued trial conduct.

15 ADMINISTRATIVE ASPECTS

15.1 *Ethics and Regulatory Compliance*

This study will be conducted according to the Integrated Addendum to ICH E6(R1): Guideline For Good Clinical Practice E6(R2) dated 9 November 2016 and local regulations.
In Australia, the study will be conducted according to the ICH Guideline for Good Clinical Practice Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice ICH E6(R2) dated 9 November 2016 annotated with TGA (Therapeutic Goods Administration) comments and in compliance with applicable laws and regulations. The study will be performed in accordance with the National Statement on Ethical Conduct in Human Research 2007 (updated 2018 and as amended from time to time), the Australian Code for the Responsible Conduct of Research (2018, and as amended from time to time), and the principles laid down by the World Medical Association in the Declaration of Helsinki 2013.
To this end, no participant will be recruited to the study until all the necessary approvals have been obtained and the participant has provided written informed consent. Further, the investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a participant. In this circumstance the NHMRC CTC, principal investigator and HREC must be advised immediately.
See Appendix 10: Ethics and Regulatory Compliance for USA Sites

15.2 *Confidentiality*

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the NHMRC CTC, University of Sydney and will only be available to people directly involved with the study and who have signed a Confidentiality Agreement.

15.3 *Protocol Amendments*

Changes and amendments to the protocol can only be initiated and made by the ITSC. Approval of amendments by the Institutional HRECs/IRBs is required prior to their implementation. Amendments to the protocol in the USA will be approved by PrECOG, their Study Chair and statistician prior to submission to the FDA. In some instances, an amendment may require a change to a consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the data collected, if required, will be incorporated in the amendment.
The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial participant(s).

15.4 *Data Handling and Record Keeping*

All trial data required for the monitoring and analysis of the study will be recorded on the eCRFs provided. All required data entry fields must be completed. Data corrections will be done according to the instructions provided. The investigator will be asked to confirm the accuracy of completed CRFs by signing key CRFs as indicated.

Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a participant's medical records, hospital charts, clinic charts, the investigator's participant study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a participant's study-related data.

The following information should be entered into the participant's medical record:

a. The participant's protocol identification.
b. The date that the participant entered the study, and participant number.
c. A statement that informed consent was obtained (including the date).
d. Relevant medical history, all concomitant medications during study participation.
e. Dates of all participant assessment and results of key trial parameters.
f. Occurrence and status of any SAEs.
g. The date the participant exited the study, and a notation as to whether the participant completed the study or reason for discontinuation.

All study-related documentation at sites will be maintained for 15 years following completion of the study, or longer as required by locally applicable laws and regulations.

US sites also please refer to Appendix 10: Ethics and Regulatory Compliance for USA Sites.

15.5 *Study Monitoring*

Data from this study will be monitored by Clinical Trials Program staff from the NHMRC CTC, PrECOG, or their delegates. Monitoring will include centralised review of CRFs and other study documents for protocol compliance, data accuracy and completeness. Monitoring may include monitoring visits to investigational sites during the study for source data verification, review of the investigator's site file and drug handling records. The NHMRC CTC in Australia and PrECOG in the USA will be given direct access to source documents, CRFs and other study-related documents. By signing the informed consent form, the participant gives authorised NHMRC CTC staff (or delegates) in Australia and PrECOG staff (or delegates) in the USA direct access to their medical records and the study data.

Representatives and agents of PrECOG and, as applicable to the study, the manufacturer of investigational product must be allowed to visit all study site locations periodically to assess the data, quality and study integrity. The purpose of this visit is to review study records and directly compare them with source documents and discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable. Monitoring of drug accountability will also occur.

US sites also please refer to Appendix 10: Ethics and Regulatory Compliance for USA Sites

15.6 *Audit and Inspection*

This study may be participant to audit or inspection by representatives of the University of Sydney, TOGA, PrECOG, AstraZeneca (AZ), MedImmune Ltd, the NHMRC CTC, relevant HRECs/IRBs or representatives of regulatory bodies [e.g. Therapeutic Goods Administration (TGA) or Food and Drug Administration (FDA)]. In the United States, the study may be evaluated by other auditors and government inspectors who must be allowed access to electronic Case Report Forms (eCRFs), source documents and other study files. The Investigator must notify their coordinating centre of any scheduled visits by regulatory authorities, and submit copies of all reports.

US sites also please refer to Appendix 10: Ethics and Regulatory Compliance for USA Sites

15.7 *Clinical Study Report*

A Clinical Study Report which summarises and interprets all the pertinent study data collected will be issued which may form the basis of a manuscript intended for publication. The Clinical Study Report or summary thereof will be provided to the study investigators, TOGA, PrECOG and AstraZeneca, and relevant

HRECs/IRBs as required. A lay summary of the results will be prepared for participants and other interested parties.
The study will be registered on ClinicalTrials.gov in compliance with 42 CFR Part 11 prior to study start, updated periodically and required documentation including results will be posted per applicable timelines according to the study primary completion date.

15.8 *Publication Policy*

The ITSC will document the publication policy for the trial. Manuscript(s) will be submitted to peer-reviewed journal(s). The first publication will be the report of the full trial results based on the main protocol generally using the study group name for large Phase II/III studies, with subsequent publications of data subsets in individual names based on contribution. A Writing Committee will be appointed and will develop a publication plan, including authorship, target journals and expected dates of publication. All publications must receive prior written approval from the ITSC, TOGA and PrECOG prior to submission.

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17 APPENDICES

17.1 *Appendix 1 Modified RECIST 1.1 Criteria for Pleural Mesothelioma*

Guidelines for measuring pleural mesothelioma as per modified RECIST 1.1

Measurement of Pleural Tumor and Other Sites at Baseline:

Definition of Measurability

- Pleural tumor is measurable if there exists at least one pleural site for which tumor thickness is ≥ 7 mm.
- Non-pleural sites of disease can determine measurability, and will have a unidimensional greatest diameter of ≥ 10 mm at baseline.
- Measurable involved lymph nodes have a short-axis measurement ≥ 15 mm at baseline.
- Pleural effusion is not considered a measurable lesion.

Measurement Sites at Baseline

- Unidimensional pleural tumor measurements should be determined by constructing a line segment perpendicular to a tangent to the curve of the pleura at the outer measurement point (Figure A). The outer measurement point is best placed on the chest wall or mediastinum, avoiding the anterior pleural reflexion.
- Image sections chosen for measurement should be readily identified at subsequent time points and ideally related to clear fixed anatomical mediastinal or chest wall landmarks (Figure B).
- Areas of pulmonary atelectasis, pleural effusion, and indistinct tumor boundaries should be avoided if possible.
- Where a measurement site is related to the pulmonary fissures, unidimensional measurements should be made perpendicular to a tangent to the pleura at that point (Figure C).
- Pleural thickness is recorded at up to two measurement sites, if possible, at each of up to three separate axial sections (levels) of the thoracic CT scan at baseline (Figures B and D). Axial sections should be at least 1 cm apart. The sum of these (up to) 6 measurements gives the baseline sum of pleural measurements.
- Each selected measurement must individually satisfy the criterion for minimally measurable disease.
- In the event of bilateral disease, the pleura is considered a single organ and pleural measurement sites may be distributed across both hemithoraces, up to three independent CT sections per hemithorax, no more than two measurement sites per section, to a total of 6 sites.
- Additional unidimensional non-pleural target lesion measurements meeting the definition of measurable disease may be made of involved lymph node sites, chest wall masses, or metastatic disease and added to the sum of pleural tumor thickness measurements to give a baseline sum of target lesion measurements. Measurements of non-pleural disease may be included from a maximum of five lesions total, and a maximum of two lesions per organ. Measurements acquired from pleural sites are to be considered a contribution from one organ.
- Other disease present at baseline should be recorded as “non-target lesions.” In the case of diffuse pleural disease, examples of descriptive notations include: “extensive pleural thickening,” “circumferential pleural

thickening," "tumor indistinguishable from diaphragm in base," "extensive pleural nodularity," or similar. This may include non-measurable disease as well as measurable but non-measured pleural disease. It is not practical to separately identify individual pleural lesions that are contiguous or exceed a reasonable number.

- Images of the baseline scan measurement segments should be stored for visual reference when measuring subsequent images.

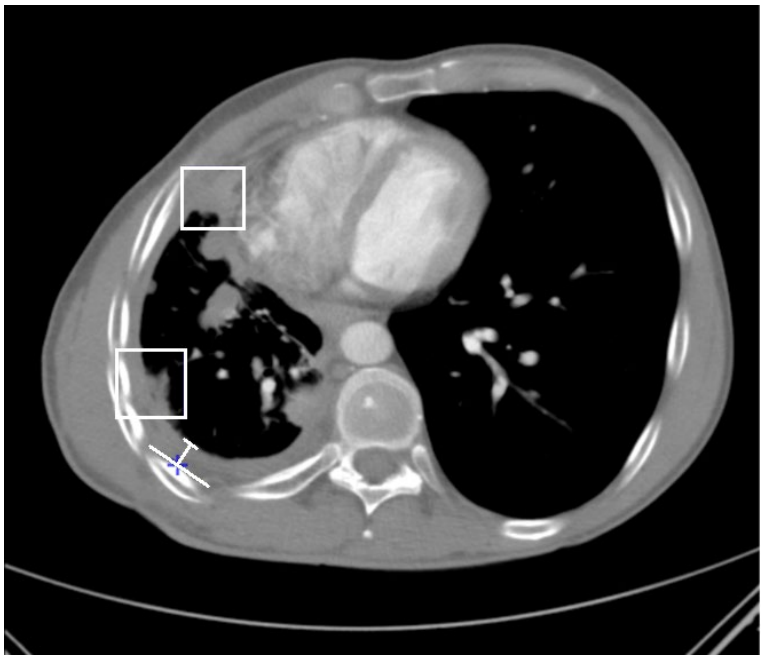
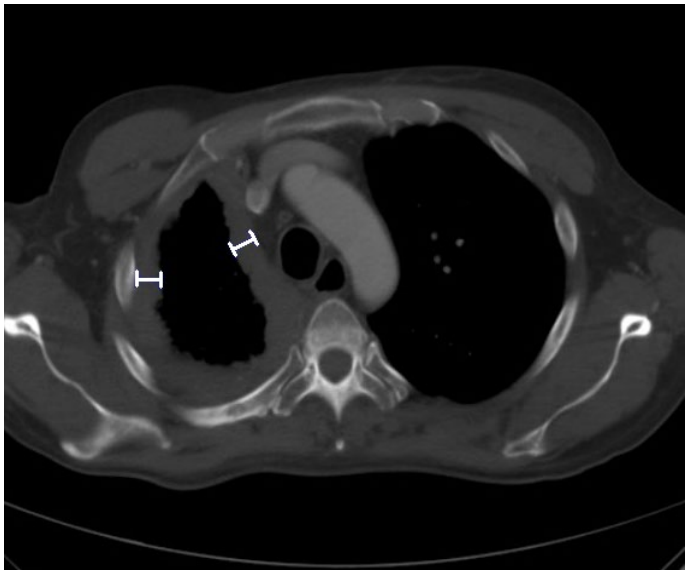
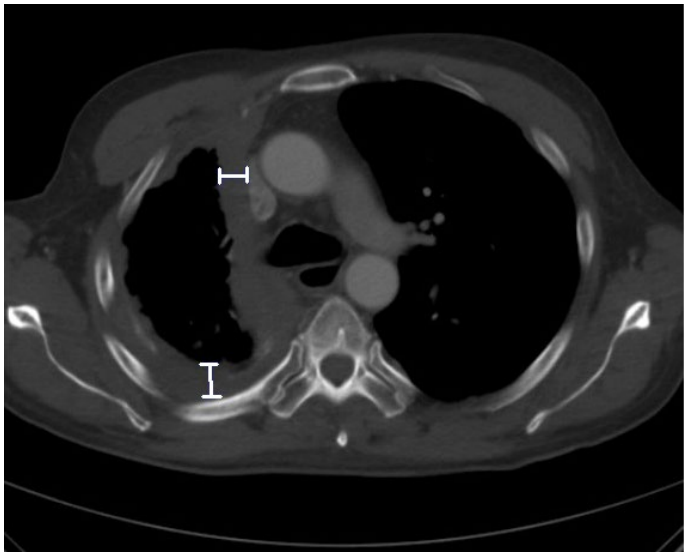


Figure A: Unidimensional measurements are determined by constructing a line segment perpendicular to a tangent to the curve of the pleura at the outer measurement point. Avoid areas of pleural reflexion or unclear disease boundaries (boxes).

(i)



(ii)



(iii)

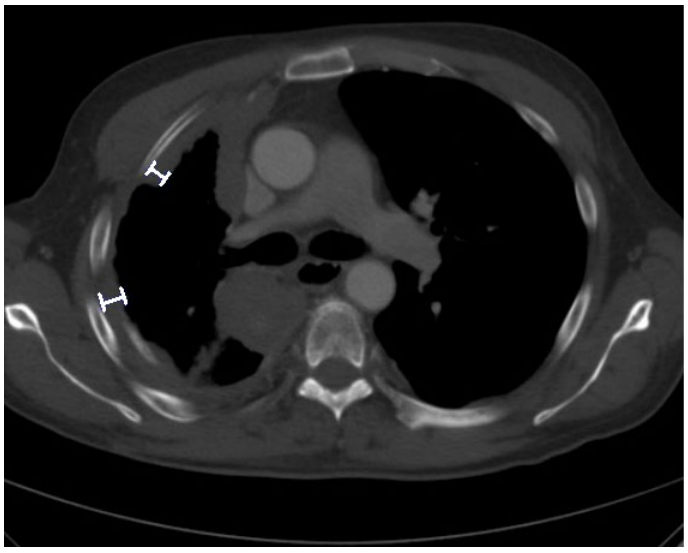


Figure B: Example of two measurements at each of three anatomically reproducible levels (i, ii, and iii).

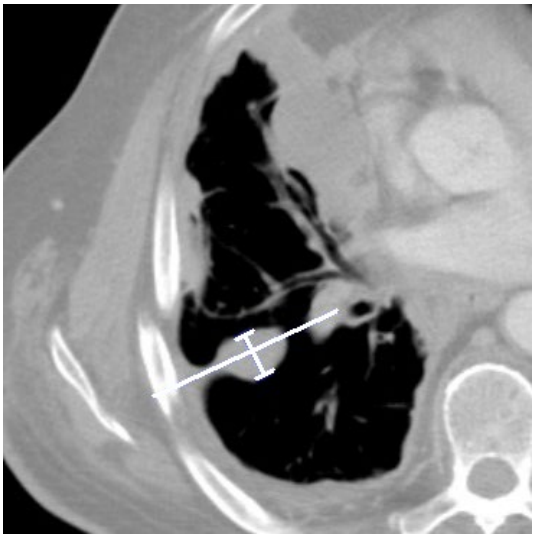


Figure C: Lesions in the pleural fissure should be measured perpendicular to the fissure at that point.

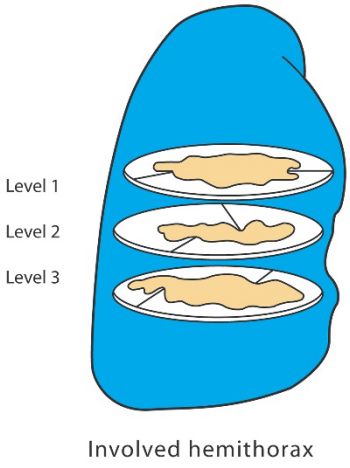
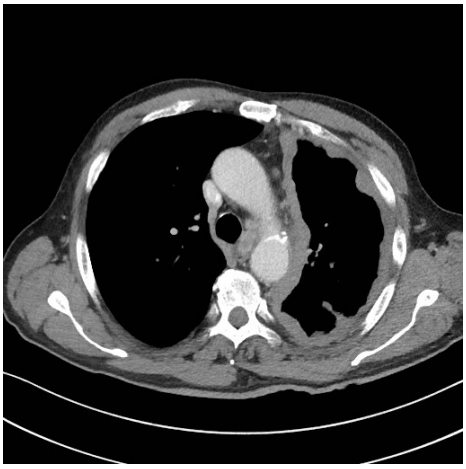


Figure D: Pleural thickness is recorded at up to two measurement sites at each of up to three separate axial sections (levels) of the thoracic CT scan at baseline. Axial sections should be at least 1 cm apart.

(i)



(ii)

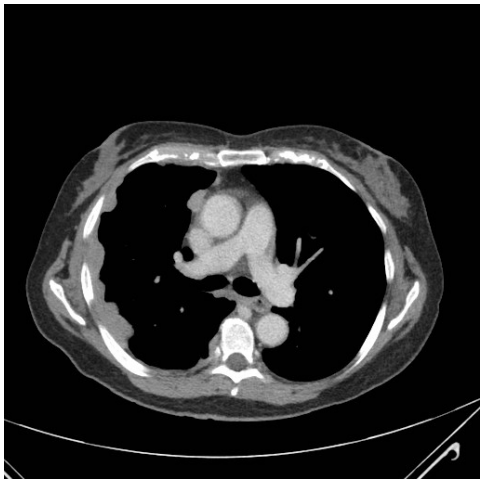


Figure E: Examples of (i) “circumferential pleural thickening” in non-target lesion descriptor and (ii) “extensive pleural nodularity” in non-target lesion descriptor.

Measurement of Disease at Subsequent Time Points:

- Pleural tumor measurements should always be performed at the same site, in the same orientation (direction), and with the same image display parameters as the baseline measurement, irrespective of changes in lesion morphology and shape. If tumor is present at a site but is too thin to measure on a magnified window, a default value of 2 mm should be used.
- Lesions that are viewed on the same image slice at baseline but are subsequently best viewed on different images slices due to alterations in thoracic contraction, respiration, or patient positioning may be measured on different slices on subsequent scans.
- Modified RECIST 1.1 recommends that the same observer acquire measurements from all CT scans from a given participant.
- Stored images of the baseline measurement line segments should be visually referenced when acquiring measurements from scans at subsequent time points.

Definitions of Objective Response:

Complete Response (CR): Disappearance of all pleural and non-pleural disease (including pleural thickening considered to represent tumor).

Partial Response (PR): Summed measurement decrease by at least 30% from the baseline scan summed measurement, which must be confirmed at a subsequent follow-up scan at least 4 weeks later (at which time the summed measurement must not exceed 70% of the baseline scan summed measurement).

Progressive Disease (PD): Summed measurement increase by at least 20% from the nadir of the summed measurements from all prior scans (up to and including the baseline scan), even if the summed measurement is $\leq$ 70% of the baseline scan summed measurement; classification as PD also requires an absolute summed measurement increase of at least 5 mm over the nadir summed measurement. An unequivocal new non-pleural lesion or an unequivocal new focus of pleural thickening that exceeds the minimum measurable size (and represents either a pleural tumor mass physically distinct from that associated with existing measurement sites or a region of a previously existing pleural tumor mass that would now unequivocally qualify as a measurement site) would be considered progressive disease[#].

Stable Disease (SD): A decrease in the summed measurement that does not qualify as PR, or an increase in the summed measurement that does not qualify as PD.

Note: Confirmation of objective response on a subsequent occasion at least 4 weeks later is required to assign a response of Confirmed PR or Confirmed CR.

An unequivocal new non-pleural lesion or an unequivocal new focus of pleural thickening that exceeds the minimum measurable size (and represents either a pleural tumor mass physically distinct from that associated with existing measurement sites or a region of a previously existing pleural tumor mass that would now unequivocally qualify as a measurement site) would be considered progressive disease; the assessment of “unequivocal,” however, requires judgment and careful review to ensure that the lesion was not present previously in an adjacent section.

Duration of Response

Duration of response will be defined as the time from the date of first documented response (CR/PR) as per mRECIST 1.1 for mesothelioma as assessed by the investigator until the date of documented progression or death in the absence of disease progression, the end of response will coincide with the date of progression or death from any cause. The time of the initial response will be defined as the latest of the dates contributing towards the first assessment response of PR or CR.

Reference: Armato SG and Nowak AK. Revised Modified RECIST Criteria for Assessment of Response in Malignant Pleural Mesothelioma (Version 1.1) Journal of Thoracic Oncology; 13(7) p 1012-1021; 2018

A detailed Radiology Manual will be provided to study sites.

17.2 *Appendix 2 ECOG Performance Status Scales*

ECOG Performance Status Scale	
Grade	Descriptions
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.

17.3 *Appendix 3 Cockcroft-Gault Formula*

Estimation and Measurement of Glomerular Filtration Rate (GFR)

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

Age = Age in years (20 to 80)
To convert serum creatinine in mg/dl to µmol/l use the following formula:
Cr (µmol/l) = Cr (mg/dl) x 88.4

17.4 *Appendix 4 Acceptable Birth Control Methods*

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

Female participant of child-bearing potential

- Female participants 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 (list below) from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy).
- Non-sterilised male partners of a female participant of childbearing potential must use male condom 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 participants should also refrain from breastfeeding throughout this period.

Male participants with a female partner of childbearing potential

- Non-sterilized male participants who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). However, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male participants should refrain from sperm donation throughout this period.
- Female partners (of childbearing potential) of male participants must also use a highly effective method of contraception throughout this period (list below).

N.B Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.
Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥ 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

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 below. 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).

Effective methods:

- Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant®
- Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing®
- Injection: Medroxyprogesterone injection: e.g. Depo-Provera®
- Combined Pill: Normal and low dose combined oral contraceptive pill
- Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra®

- Minipill: Progesterone based oral contraceptive pill using desogestrel: i.e. Cerazette®
- Copper T intrauterine device
- Levonorgestrel-releasing intrauterine system: e.g. Mirena®

17.5 *Appendix 5 Management of Immune-mediated Adverse Events (ImAEs), infusion-related reaction and non-immune related reactions*

General Considerations Regarding Immune-Mediated Reactions
These guidelines are provided as a recommendation to support investigators in the management of potential immune-mediated 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., NCCN, 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 immune-mediated adverse events (imAEs) are essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse events. 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, immunotherapy should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents such as TNF inhibitors (e.g., infliximab) 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 need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and 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.

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

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** – Monitor patients for signs 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 aetiologies 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, 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.	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated, consider chest CT with contrast and repeat in 3-4 weeks. – 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

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		(,10mg prednisone or equivalent)	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. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with Clinical Study Lead, as needed
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – 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. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General Guidance	**For Any Grade** – 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). – **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.**

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for *Clostridium difficile* toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade 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; 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 (,10mg prednisone, or equivalent.	**For Grade 2** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 2 to 3 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consult a gastrointestinal (GI) specialist for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg IV methylprednisolone, promptly start immunosuppressants 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

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			or relevant practice guidelines. [a] **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 patient treated with PDL-1 inhibitors, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper. Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days. • Permanently discontinue study drug for 1) Grade 3 colitis in patients treated with CTLA-4 inhibitors or 2) Any grade of intestinal perforation in any patient treated with immune checkpoint inhibitor (ICI). Grade 4 Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 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.**

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Hepatitis (elevated LFTs) 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** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1	• No dose modifications. • If it worsens, then consider holding therapy.	**For Grade 1** – Continue LFT monitoring per protocol.
	Grade 2	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline and there was no elevation in bilirubin. resume study drug/study regimen after completion of steroid taper (<10mg prednisone or equivalent). • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.b	**For Grade 2** – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until LFT elevations improve or resolve. – If no resolution to Grade ≤1 in 1 to 2 days, consider discussing with clinical study lead, as needed. – If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients	**Grade 3 or 4**	For Grade 3 Hold study drug/study regimen for elevations in transaminases ≤8 × ULN (and no elevation in bilirubin), or elevations in bilirubin ≤5 × ULN until resolution to grade <1 or baseline: • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper (<10mg prednisone or equivalent). • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days • Permanently discontinue study drug/study regimen for elevations in transaminases >8 × ULN or any elevations in bilirubin >5 × ULN. For Grade 4 Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – 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 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.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Hepatitis (elevated LFTs) 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** See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	**Any Elevations of AST, ALT, or TB as Described Below**	**General Guidance**	**For Any Elevations Described** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg. – For HCV+ patients: evaluate quantitative HCV viral load. – Consider consulting 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 HBcAb+: Evaluate for both HBV and HCV as above.
	Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline	• No dose modifications. • If ALT/AST elevations represent significant worsening based on investigator assessment, then treat as described for elevations in the row below. • For all transaminase elevations, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
	Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN. • If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤5.0×ULN, resume study drug/study regimen after completion of steroid taper (<10mg prednisone or equivalent). • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with 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 immunosuppressants (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines).[a] Discuss with clinical study lead if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN. Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN within 14 days and after completion of steroid taper (<10mg prednisone or equivalent). • Permanently discontinue study drug/study regimen if the elevations do not	– 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 immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an immunosuppressant (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with a hepatologist or relevant practice

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		downgrade to AST or ALT ≤5.0×ULN within 14 days	guidelines). Discuss with clinical study lead if mycophenolate is not available. **Infliximab should NOT be used.**
	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen.	– **Same as above (except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): **Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase rise** - **For example, manage dosing for second level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)** - **For the third and fourth levels of transaminase rises, permanently discontinue study drug/study regimen**			
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Consult a nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decreased urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). – Consider using steroids in the absence of a clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade events.
	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.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			• If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper (<10mg prednisone or equivalent).	**For Grade 2** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent beyond 3 to 5 days or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, 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. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant in consultation with a nephrologist.
Rash or Dermatitis **(Including Pemphigoid)**	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for definition of	**General Guidance**	**For Any Grade** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – **HOLD STUDY DRUG IF STEVENS-JOHNSON SYNDROME (SJS), TOXIC EPIDERMAL NECROLYSIS (TEN), OR OTHER SEVERE CUTANEOUS ADVERSE REACTION (SCAR) IS SUSPECTED.**

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
	severity/grade depending on type of skin rash)		– **PERMANENTLY DISCONTINUE STUDY DRUG IF SJS, TEN, OR SCAR IS CONFIRMED.**
	Grade 1	No dose modifications.	**For Grade 1** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emollient, lotion, or institutional standard).
	Grade 2	For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10mg prednisone or equivalent).	**For Grade 2** – Obtain dermatology consult. – 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 3 days 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. – Consider skin biopsy if the event persists for >1 week or recurs.
	Grade 3 or 4	**For Grade 3** • Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper	**For Grade 3 or 4** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. Consider, as necessary, discussing with clinical study lead.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		(<10mg prednisone or equivalent). • If toxicity worsens, then treat as Grade 4. **For Grade 4** Permanently discontinue study drug/study regimen.	
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Consider consulting an endocrinologist for endocrine events. – Consider discussing with clinical study lead, as needed. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). 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.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
	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 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 other than hypothyroidism and type 1 diabetes mellitus, 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 (<10mg prednisone or equivalent). • Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be	**For Grade 2, 3, or 4** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, and without corticosteroids. **Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis**. – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		retreated with study drug/study regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement.	
Amylase/Lipase increased	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – 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 pancreatic 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** – Consider Gastroenterology referral

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
	Grade 2, 3, or 4	**For Grade 2 or 3** Hold study drug/study regimen dose until resolution to Grade ≤1. If toxicity improves to Grade <1 or baseline, then resume study drug/study regimen after completion of steroid taper (<10mg prednisone, or equivalent). **For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 2, 3, or 4** – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – IV hydration
Neurotoxicity (to include but not be limited to non-infectious meningitis, non-infectious encephalitis, and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (Depending on the type of neurotoxicity, refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate. – **FOR TRANSVERSE MYELITIS, PERMANENTLY DISCONTINUE FOR ANY GRADE.**
	Grade 1	No dose modifications.	**For Grade 1** – See “Any Grade” recommendations above.
	Grade 2	• For acute motor neuropathies or	**For Grade 2** – Consider, as necessary, discussing with the clinical study lead.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. • For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if Grade 2 imAE does not resolve to Grade ≤1 within 30 days.	– Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with an additional immunosuppressant (e.g., IV IG or other immunosuppressant depending on the specific imAE).
	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. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite IV corticosteroids, consider additional workup and promptly treat with an additional immunosuppressant (e.g., IV IG or other immunosuppressant depending on the specific imAE).
Peripheral neuromotor syndromes	**Any Grade** (Refer to NCI CTCAE applicable version in study	**General Guidance**	**For Any Grade** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
(such as Guillain-Barre and myasthenia gravis)	protocol for defining the CTCAE grade/severity)		Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and “repetitive stimulation” if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1** – Consider discussing with the clinical study lead, as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Consult a neurologist.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30	**For Grade 2** – Consider discussing with the clinical study lead, as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		days or if there are signs of respiratory insufficiency or autonomic instability.	– Consult a neurologist. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. o Avoid medications that can worsen myasthenia gravis (e.g. some antibiotics, beta blockers, calcium channel blockers, muscle relaxants). *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4	**For Grade 3 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.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			MYASTHENIA GRAVIS: ○ Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. ○ If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. ○ Avoid medications that can worsen myasthenia gravis (e.g. some antibiotics, beta blockers, calcium channel blockers, muscle relaxants). *GUILLAIN-BARRE:* ○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
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** – 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.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			– Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 2, 3 or 4	• If Grade 2-4 myocarditis, permanently discontinue the study drug/study regimen. • **For any grade immune-mediated myocarditis that is biopsy proven, discontinue the drug permanently. **	**For Grade 2-4** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg 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. 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** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			– 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. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1	• No dose modifications.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the clinical study lead.
	Grade 2	• Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if it	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the clinical study lead.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	– 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 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.**
	Grade 3 or 4	**For Grade 3** • Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4** • Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Monitor symptoms closely; recommend hospitalization. – Obtain 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.** – Consider whether patient may require IV IG, plasmapheresis.

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

[b]FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.
[c]NCCN Clinical Practice Guidelines in Oncology "Management of Immunotherapy-Related Toxicities" Version 1.2020 – December 2019

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

Other Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC 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).	**For Any Grade** – The clinical study lead may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section – Thorough evaluation to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) – Consultation with relevant specialist – Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	– Monitor as clinically indicated
Grade 2	– Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. – If toxicity worsens, then treat as Grade 3 or Grade 4. – Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. – Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper.	**For Grade 2, 3, or 4** – Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines (e.g., NCCN, ESMO)
Grade 3	Hold study drug/study regimen	
Grade 4	Permanently discontinue study drug/study regimen	

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

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC 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 prior to subsequent doses. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Manage severe infusion-related reactions per institutional standards appropriate clinical practice guidelines, and society guidelines.

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

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

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

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

List of Abbreviations

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

17.6 *Appendix 6 Common Terminology Criteria for Adverse Events (CTCAE)*

Adverse events and/or adverse drug reactions will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

17.7 *Appendix 7 iRECIST as applied to Pleural Mesothelioma*

As stated in Armato SG and Nowak AK. Revised Modified RECIST Criteria for Assessment of Response in Malignant Pleural Mesothelioma (Version 1.1) Journal of Thoracic Oncology; 13(7) p 1012-1021; 2018:
"The key principles of iRECIST require no changes to the measurement approach, concepts of objective tumor response, or the management of lymph nodes, but iRECIST does allow for patients to continue on clinical trials through initial progression of baseline target lesions or the development of new lesions and introduces the concept of "unconfirmed progressive disease" (iUPD) and "confirmed progressive disease" (iCPD)."
"*As iRECIST does not alter any tumor response considerations that are unique to pleural mesothelioma, mRECIST 1.1 recommends adoption of the principles of iRECIST for immunotherapy clinical trials where pseudoprogression and delayed response may be a consideration. Hence, if continued treatment upon initial iUPD is considered clinically safe and appropriate, subsequent iCPD within 4-8 weeks would be required to confirm progression and cease study treatment. Specific guidance included in the study protocol should incorporate the principles of mRECIST 1.1 (including selection of measurement sites, number of sites, and measurable disease guidance) together with the principles of iRECIST as applied to progressive disease*".
As per this guidance, objective response will also be assessed using the principles of iRECIST in the context of tumour measurements performed as per Modified RECIST 1.1 guidelines (51). Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, resulting in previously undetectable lesions becoming detectable. The criteria are identical to those of mRECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumour burden, or the appearance of new lesions, does not reflect true tumour progression.
Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

NOTE: In order to have confirmed objective disease progression, there should be two consecutive assessments meeting the PD definition:
- the first PD by modified RECIST 1.1 for mesothelioma AND
- the second PD using the confirmation of progression criteria (above).

If the first assessment fulfilling the PD definition by modified RECIST 1.1 for mesothelioma is not confirmed, continue with assessments until the next PD by modified RECIST 1.1 for mesothelioma, which in turn will need its own immediate subsequent confirmation scan. In the absence of significant clinical deterioration, treatment with study drug may continue between the initial assessment of progression and the scan to confirm progression.

If the confirmation scan confirms progression, then the date of the prior scan with PD should be declared as the date of progression.
If progression is not confirmed, in the absence of significant clinical deterioration, then the patient should continue study drug and on-treatment assessments until the next PD which will also require a follow-up confirmation scan. **If the first PD is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan.**
If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) prior to radiologic progression, then the patient should still continue to be followed until confirmed objective disease progression.

Confirming Progression
Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.
iCPD is confirmed if further progression, compared to the last assessment, is seen as evidenced by one or more of the following

- Continued progression where mRECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions (from uPD)
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum

  - Continued unequivocal progression in non-target disease with an increase in tumour burden
  - Increase in size of previously identified new lesion(s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions)
- mRECIST 1.1 criteria are met where progression was not previously identified, including the appearance of additional new lesions

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in Table 2, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented.

New Lesions

New lesions should be assessed and measured as they appear using mRECIST 1.1 criteria (maximum of 6 pleural unidimensional sites, no more than 2 per extra pleural site, at least 7 mm for pleural measurement sites, and 10 mm in long axis for non-pleural lesions (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form. These data will enable the development and testing of alternate response criteria, or further modifications of RECIST.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Table 1: Time-point (TP) iResponse

Pleural measurement sites and Target Lesions*	**Non-Target Lesions***	**New Lesions***	**Time Point Response**	
			No prior iUPD**	Prior iUPD**
CR / iCR	CR	No	CR	iCR
CR/iCR	Non-CR/Non-PD Non-iCR/Non-iUPD	No	PR	iPR
PR/iPR	Non-CR/Non-PD Non-iCR/Non-iUPD	No	PR	iPR
SD/iSD	Non-CR/Non-PD Non-iCR/Non-iUPD	No	SD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	The appearance NLs confirms PD if ○ Additional NLs or ○ iUPD in last TP based on NLs and increase in size (≥ 5mm for NLT or any increase for NLNT) If no change in NLs from last TP, remains iUPD

PD	Non-CR/Non-PD Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in sum of at least 5mm, otherwise remains iUPD
PD	PD	No	iUPD	iCPD if further increase in previously identified*** T lesion iUPD ≥ 5mm and / or NT lesion iUPD
PD	PD	Yes	iUPD	iCPD if further increase in previously identified T lesion iUPD ≥ 5mm and / or NT lesion iUPD and / or size or number of new lesion
Non-iUPD	Non-iUPD	Yes	iUPD	iCPD if increase in size of previously identified new lesions of increased number of new lesion
* Using RECIST 1.1 principles. If no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same ** in any category *** previously identified in assessment immediately prior to this time-point NA = not applicable				

Table 2: iRECIST Best Overall Response (iBOR)
All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

Time Point Response 1 (TPR1)	Time Point Response 2 (TPR2)	Time Point Response 3 (TPR3)	Time Point Response 4 (TPR4)	Time Point Response 5 (TPR5)	iRECIST Best Overall Response (iBOR)
CR	CR, PR, iUPD, NE	CR/iCR, PR/iPR, iUPD, iCPD, NE	iUPD	iCPD	iCR
iUPD	PR, SD, NE	CR	CR, PR, SD, iUPD, NE	CR, PR, SD, iUPD, iCPD, NE	iCR
iUPD	PR	PR, SD, iUPD, NE	PR, SD, iUPD, NE, cPD	PR, SD, iUPD, NE, iCPD	iPR
iUPD	SD, NE	PR	PR, SD, iUPD, NE	PR, SD, iUPD, iCPD, NE	iPR
iUPD	SD	SD, iUPD, NE	SD, iUPD, iCPD, NE	SD, iUPD, iCPD, NE	iSD
iUPD	iUPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD
1) Table assumes a randomized study where confirmation of CR or PR is not required 2) NE = not evaluable that cycle 3) Designation "I" for BOR can be used to indicate prior uPD to aid in data interpretation 4) For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation					

Response and Stable Disease Duration (mRECIST 1.1 and iRECIST)
Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).
Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

Tumour measurements are all uni-dimensional as measured for modified RECIST for PM.

17.8 *Appendix 8 EORTC QLQ-C30*



EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: □□□□

Your birthdate (Day, Month, Year): □□□□□□□□

Today's date (Day, Month, Year): 31 □□□□□□□□

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

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During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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EORTC QLQ – LC29

ENGLISH

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	Have you coughed?	1	2	3	4
32.	Have you coughed up blood?	1	2	3	4
33.	Have you been short of breath when you rested?	1	2	3	4
34.	Have you been short of breath when you walked?	1	2	3	4
35.	Have you been short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had problems swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
43.	Have you had allergic reactions?	1	2	3	4
44.	Have you had burning or sore eyes?	1	2	3	4
45.	Have you been dizzy?	1	2	3	4
46.	Have you had splitting fingernails or toenails?	1	2	3	4
47.	Have you had skin problems (e.g. itchy, dry)?	1	2	3	4
48.	Have you had problems speaking?	1	2	3	4

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Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
49. Have you been afraid of tumor progression?	1	2	3	4
50. Have you had thin or lifeless hair as a result of your disease or treatment?	1	2	3	4
51. Have you been worried about your health in the future?	1	2	3	4
52. Have you had dry cough?	1	2	3	4
53. Have you experienced a decrease in your physical capabilities?	1	2	3	4
54. Has weight loss been a problem for you?	1	2	3	4

Please answer the following questions only if you had surgery for lung cancer:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
55. Have you had pain in the area of surgery?	1	2	3	4
56. Has the area of your wound been oversensitive?	1	2	3	4
57. Have you been restricted in your performance due to the extent of surgery?	1	2	3	4
58. Have you had any difficulty using your arm or shoulder on the side of the chest operation?	1	2	3	4
59. Has your scar pain interfered with your daily activities?	1	2	3	4

Were there any symptoms or problems that were not covered by the questionnaire, but were relevant for you in the past week?

60. _____	1	2	3	4
61. _____	1	2	3	4
62. _____	1	2	3	4

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17.9 *Appendix 9 Euroqol 5 item preference-based measure of health (EQ-5D-5L)*

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

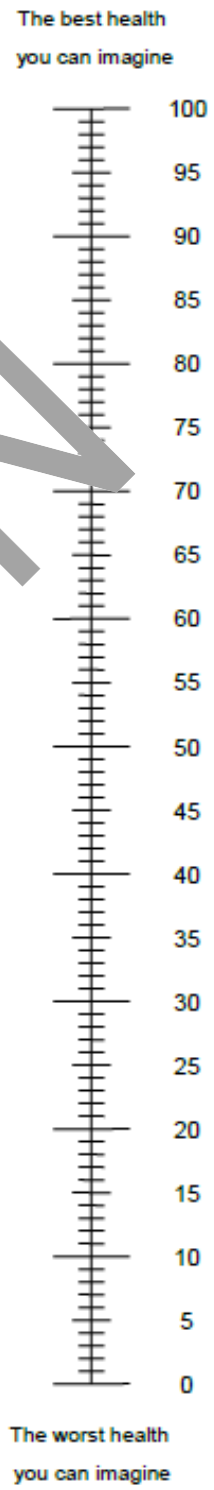
- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

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- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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17.10 *Appendix 10 Ethics and Regulatory Compliance for USA Sites*

PrE0506

IND#: 152284

PrECOG PM: [redacted]

PrECOG, LLC
1818 Market Street
Suite 3000
Philadelphia, PA 19103
Phone: 215-789-7001
Email: DREAM3R@precogllc.org

PrECOG will recruit sites in the United States (US) and oversee US site activities. US investigators must follow all aspects of the protocol, unless otherwise specified in this Appendix, which includes additional practical and administrative aspects of the protocol specific to sites/investigators in the US.

US sites should refer to information provided by PrECOG in site activation documents for specific details concerning Institutional Review Board (IRB) approvals, Informed Consent procedures, regulatory requirements, medical monitoring, serious adverse event reporting, data collection, and monitoring.

1. Ethics

This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with applicable US regulatory requirements and International Conference on Harmonization/Good Clinical Practice (ICH/GCP).

The investigator will ensure that the basic principles of “Good Clinical Practice” as outlined in the current version of 21 Code of Federal Regulations, subchapter D, part 312, “Responsibilities of Sponsors and Investigators”, part 50, “Protection of Human Subjects”, and part 56, “Institutional Review Boards”, are adhered to.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the patient informed consent will receive Institutional Review Board (IRB) approval prior to initiation of the study.

2. Site Institutional Review Board

Before study initiation, the Investigator or group of investigators at a clinical site must have written and dated approval from their respective IRB of record for the protocol, site-specific consent form(s), patient materials (e.g. Quality of Life forms or instructions) and any other written information to be provided to patients. The Investigator should also provide the IRB with a copy of the current and all future Investigator Brochures or product labelling.

The Investigator should provide the IRB with reports, updates, and other information (e.g., Safety Updates, amendments, and administrative letters) according to regulatory requirements, IRB or study site procedures.

3. Informed Consent Procedures

Current Food and Drug Administration (FDA), state, federal and institutional regulations concerning informed consent will be followed.

Investigators must ensure that patients who volunteer for clinical trials or their legally acceptable representative are clearly and fully informed about the purpose, potential risks and other information.

Appropriate protocol specific informed consent form (ICF) templates will be provided to sites. Preparation of the site-specific consent form is the responsibility of the site Investigator and must include all applicable regulatory and IRB requirements, and must adhere to Good Clinical

Practices (GCP) and to the ethical principles that have their origin in the Declaration of Helsinki. All changes to the ICF template will be approved by PrECOG and/or their representatives prior to implementation.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the consent process will also include written authorization by patients to release medical information to allow National Health and Medical Research Council (NHMRC) Clinical Trials Centre (CTC), PrECOG and/or its agents, regulatory authorities, and the IRB of record at the study site for access to patient records and medical information relevant to the study, including the medical history. This will be documented in a site approved format obtained at the time of informed consent per institutional policies. This form should also be submitted to PrECOG and/or its agents for review prior to its implementation and be available for reviews at site monitoring visits.

The Investigator must provide the patient or legally acceptable representative with a copy of the consent form and written information about the study in the language in which the patient is most proficient. The language must be non-technical and easily understood. The Investigator should allow time necessary for patient or patient's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the patient or the patient's legally acceptable representative and by the person who conducted the informed consent discussion. The patient or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study patients prior to patient's participation in the trial. The investigator is responsible for assuring adequate documentation of this process and for storage and maintenance of the original signed consent form for each patient/subject.

The informed consent and any other information provided to patients or the patient's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the patient's consent, and should receive IRB approval prior to use. The Investigator, or a person designated by the Investigator should inform the patient or the patient's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the patient's willingness to continue participation in the study. This communication should be documented in the patient record. During a patient's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the patient.

4. Regulatory Requirements

Before a site may enroll patients, protocol-specific regulatory and other documents must be submitted to PrECOG as noted in study materials. Detailed information regarding document submission and control is provided to each site in separate study materials.

Once required documents are received, reviewed, and approved by PrECOG or their representative, study materials will be forwarded to the site. Any changes to site regulatory documents must be submitted by the investigator to the responsible party in a timely manner. Initial study drug shipment will not occur until the regulatory packet is complete. Once PrECOG activates a site, enrollment may occur.

Prior to registration in the clinical database, all patients must have signed an appropriate consent form and HIPAA authorization form (if applicable). No patients will begin protocol therapy without formal registration per Section 5.4.2: Randomisation and instructions.

5. Medical Monitor Coverage

The PrECOG Medical Monitor will provide coverage for time-sensitive issues (i.e., eligibility, safety, etc.) in the US. For all other coverage, NHMRC CTC Medical Contact will provide Medical Monitoring oversight for all sites in the US and Australia/New Zealand.

PrECOG Medical Monitor information will be provided in separate materials to the US sites.

6. Adverse Event (AE) Reporting

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents. Please refer to Section 9 Safety Reporting.

7. Serious Adverse Event (SAE) Reporting

SAE reporting per Section 9.4: Reporting of Serious Adverse Events (including SUSARs, SSIs and USMs). PrECOG will have accountability for both initial and follow-up reporting of SAEs to the regulatory authorities within FDA reporting requirement timelines.

Serious and unexpected suspected adverse reaction and unexpected fatal or life-threatening suspected adverse reaction reports:

PrECOG will notify the FDA as soon as possible but in no case later than 7 calendar days after the initial receipt of the information.

Investigators should also report event(s) to their IRB as required.

Investigators will also be notified of all AEs that are serious, unexpected, and definitely, probably, or possibly related to the investigational product. Upon receiving such notices, the Investigator must review and retain the notice with the Investigator Brochure and submit a copy of this information to the IRB according to local regulations. The Investigator and IRB will determine if the informed consent requires revision. The Investigator should also comply with the IRB procedures for reporting any other safety information. All revisions should be submitted to PrECOG and/or agents for review.

8. Drug Supply

Refer to Section 12 Study Treatment Supply and Accountability.

Durvalumab will be provided free of charge by AstraZeneca. All other drugs are commercial stock and not supplied by the study.

9. Medidata Rave

Data collection for this study will be done through Medidata Rave. Access to this trial in RAVE will be granted by NHMRC CTC after approval by PrECOG.

De-identified radiology reports and images for tumour assessments will be uploaded to the database for all study participants. Instructions will be provided per Section 15.4 Data Handling and Record Keeping and study Radiology Manual.

10. Quality of Life and Health Resources

US sites will participate in the Quality of Life component of the study.

US sites will not participate in the Health Resources component of the study.

11. Research Sample Submission

PATIENT CONSENT: Samples are to be submitted for research studies from patients who consent to allow their tissue and blood to be submitted for research.

Refer to the Biospecimen Sampling Manual for details and procedures.

Laboratory kits will be provided by Cenetron in the US after site activation. Research laboratory samples will be batched and shipped to John Hopkins University upon request. Separate instructions will be provided to sites for shipment of stored samples.

12. Monitoring

Representatives and agents of PrECOG and, as applicable to the study, the manufacturer of investigational product must be allowed to visit all study site locations periodically to assess the data, quality and study integrity. The purpose of this visit is to review study records and directly compare them with source documents and discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable. Monitoring of drug accountability will also occur.

13. Audit & Inspections

The study may be evaluated by other auditors and government inspectors who must be allowed access to electronic Case Report Forms (eCRFs), source documents and other study files. The Investigator must notify PrECOG of any scheduled visits by regulatory authorities, and submit copies of all reports. Information as to who investigators should notify of an audit or where to address questions will be provided in additional study materials.

14. Study Records

An Investigator is required to maintain adequate regulatory files with corresponding communication and approvals, accurate histories, observations and other data on each individual treated. Data reported on the eCRFs must be consistent with the source documents as part of the patient record.

The confidentiality of records that could identify patients must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

A study specific signature record will be maintained to document signatures and initials of all persons at a study site who are authorized to make entries and/or corrections on eCRFs as well as document delegation of other study-specific roles.

15. Record Retention

The Investigator must retain investigational product disposition records, copies of eCRFs (or electronic files), and source documents for 15 years per protocol or the maximum period required by applicable regulations and guidelines, or Institution procedures, whichever is longer. The Investigator must contact PrECOG and/or representatives prior to destroying any records associated with the study.

Information as to who investigators should contact for questions will be provided in additional study documents, and representatives of PrECOG will notify the Investigator when the trial records for this study are no longer needed.

Refer to Protocol Section 15.4: Data Handling and Record Keeping for further details.