PrE0506 (DREAM3R) Statistical Analysis Plan (SAP)

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

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THE UNIVERSITY OF SYDNEY

NHMRC Clinical Trials Centre

DREAM3R
Statistical Analysis Plan

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1 ADMINISTRATION

1.1 TITLE AND TRIAL REGISTRATION

1.1.1 Descriptive title

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

1.1.2 Trial registration number

Registration ID: NCT04334759 *https://classic.clinicaltrials.gov/ct2/show/NCT04334759*

Other study IDs: CTC 0231 / TOGA 18/001 / PrE0506

1.2 SAP VERSION

1.2.1 Version history

Protocol version	SAP version	Date	Changes made	Authors
1.0	0.1	Aug 2020	Initial SAP	C. Brown
4.0	0.2	Jan 2023	Allowance for Protocol V4	C. Brown
5.0	0.9	May 2024	Changes due to early stopping	C. Brown
5.0	1.0	Oct 2024	Adding translational subgroup	C. Brown

1.2.2 Contributors to the statistical analysis plan

This statistical analysis plan has been prepared based on Australian Clinical Trials Alliance templates (*https://clinicaltrialsalliance.org.au/resource/statistical-analysis-plan/*) and JAMA guidelines[1].

Name	Affiliation	Role on study	SAP contribution
[redacted]	University of Sydney	Study Statistician	Main author

1.3 APPROVALS

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with ICH-E9 principles and, in particular, confirm that this analysis plan was developed in

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a completely blinded manner (i.e. without knowledge of the effect of the intervention(s) being assessed).

	Australia	United States
Statisticians	[redacted] Digitally signed by [redacted] [redacted] Statistician, NHMRC Clinical Trials Centre	[redacted] [redacted] Statistician, PrECOG
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Deputy Study Chairs	[redacted] [redacted] The Prince Charles Hospital DocuSigned by: [redacted] [redacted] Princess Alexandra Hospital	[redacted] [redacted] Sidney Kimmel Comprehensive Cancer Center Johns Hopkins University
Clinical Research Leads	[redacted] [redacted] Oncology Co-Director, NHMRC Clinical Trials Centre	[redacted] PrECOG CEO and Chair, PrECOG Board of Managers

2 INTRODUCTION

2.1 BACKGROUND AND RATIONALE

2.1.1 Synopsis of trial

Standard first line chemotherapy in unresectable malignant pleural mesothelioma (MPM) consists of cisplatin/carboplatin and pemetrexed. This provides a median overall survival of 12.1 months,

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progression free survival (PFS) of 5.7months (PFS at 6 months (PFS6) of 48%) and a response rate of 41%. Most 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 recent 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%.

The DREAM3R study planned to enrol 480 patients, comparing provide a median survival of 15 months in the control group and a median survival of 21.4 months in the durvalumab group (target hazard ratio of 0.70).

2.1.1.1 Protocol Version 4

The CheckMate 743 study (CM743) published results demonstrating benefit of nivolumab plus ipilimumab over chemotherapy. The DREAM3R study was modified to allow nivolumab plus ipilimumab as an alternative option in the control arm.

Eligibility criteria were restricted to include only participants with epithelioid histology as CM743 demonstrated clear benefit for non-epithelioid histology (HR 0.46, 95% CI 0.31-0.68). In epithelioid tumours, benefit of nivolumab plus ipilimumab remained uncertain, HR 0.86, 95% CI 0.69-1.08.

2.1.1.2 Protocol Version 5

After premature stopping of recruitment after 214 participants, the decision was made to revert the primary analysis population to those randomised into the chemotherapy control stratum. The small number of participants randomised into the immunotherapy control stratum will be reported as part of a combined secondary analysis, as well as separately.

2.2 OBJECTIVES

2.2.1 Hypothesis

To determine the effectiveness of adding durvalumab to standard first line chemotherapy with cisplatin/carboplatin and pemetrexed in advanced MPM.

3 STUDY METHODS

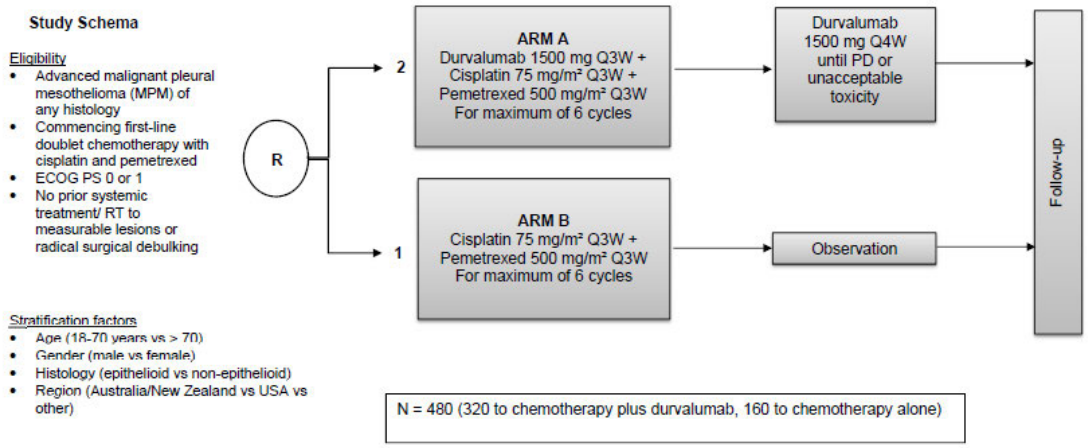
3.1 TRIAL DESIGN

3.1.1 Brief description of trial design

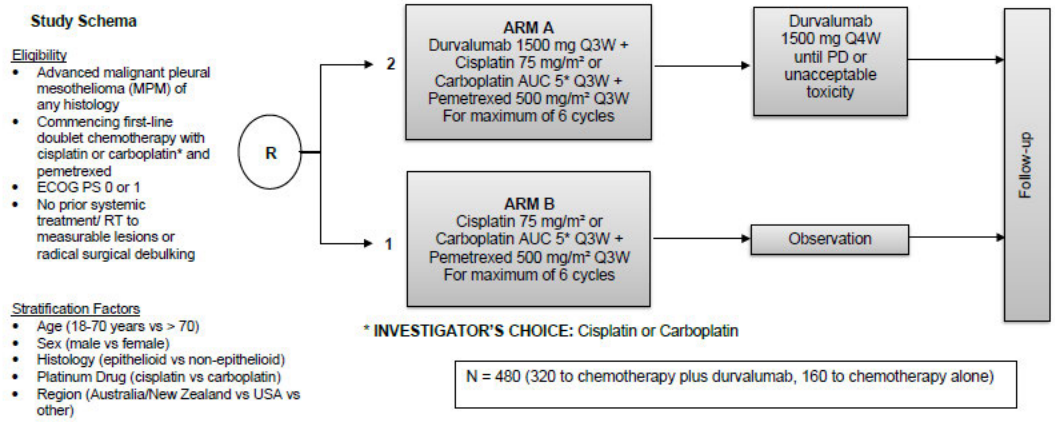
Open label, randomised, phase 3 trial.

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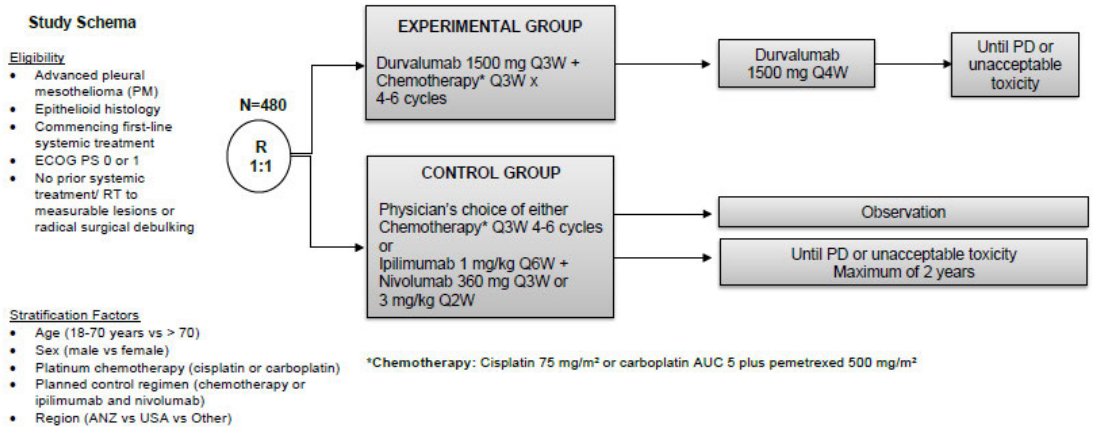
3.1.1.1 Schema - Protocol V1



3.1.1.2 Schema - Protocol V3



3.1.1.3 Schema - Protocol V4



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3.2 RANDOMISATION

3.2.1 Randomisation details

Randomisation performed within the Medidata database system using stratified permuted blocks. Candidate blocks were securely stored within medidata system and not accessible by any study team members.

- Protocols 1-3 were randomised in 2:1 ratio (intervention:control). Permuted blocks for were generated for each strata combination with random lengths of 6 and 9.
- Protocol 4 was randomised 1:1. Permuted blocks were generated in 1:1 allocations with random lengths of 4 and 6.

3.2.2 Stratification details

Stratification was initially:

1. **Age (18-70 years vs. older than 70)**
2. **Sex (male vs. female)**
3. **Histology (epithelioid vs. non-epithelioid)** ***[Protocols V1-3]***
4. **Region (Australia/New Zealand vs. USA vs. other)**

In protocol V3, type of planned platinum therapy was added as a stratification. Permuted blocks for were generated for each strata combination with random lengths of 6 and 9.

5. **Platinum Drug (cisplatin vs. carboplatin)** ***[Protocols V3-4]***

In protocol V4, histology was removed (participants were restricted to epithelioid) and an additional strata (6) was added.

6. **Planned control arm (chemotherapy vs. nivolumab+ipiluminnab,** ***[Protocol V4].***

3.3 SAMPLE SIZE

3.3.1 Full sample size calculation

Study recruitment closed prematurely with 214/480 randomised participants.

3.3.1.1 Initial calculation

The study was planned to enrol 480 patients (randomised 2:1) over 27 months and follow up for at least 24 months, providing >85% power assuming a median survival of 15 months in the control group and a median survival of 21.4 months in the durvalumab group (target hazard ratio of 0.70).

The alternate hypothesis (difference) was to be tested against the null hypothesis (no difference) with 2-sided alpha of 0.05. There was an allowance for up to 6% non-compliance due to expected use of immunotherapy in the control group after progression. This rate was to be monitored during the study and consideration given to increasing the sample size if the rate was substantially higher than expected.

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3.3.1.2 Changes at time of Protocol V4

With the change to eligibility criteria and the introduction of combination immunotherapy control arm option, the assumptions for the sample size calculation were slightly modified. The changes respected the original study total sample size (resource limitation) and required a change to a 1:1 allocation ratio.

The study was to enrol a total of 480 participants. The initial randomisation ratio of 2:1 (experimental: control) was changed to 1:1. This was to result in approximately 260 participants in the experimental group and 220 in the control group. The sample size assumptions were as follows. Participants accrued over 33 months, with follow-up for at least an additional 18 months.

This would provide >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 is due to the transition to pure epithelioid disease. The alternate hypothesis (difference) will be tested against the null hypothesis (no difference) with a study-wide, 2-sided alpha of 0.05. There is an allowance of approximately 8% for lost to follow up and/or missing data. The final analysis (312 events) was to be conducted with alpha=0.049 and have power of 85% if the HR=0.70.

3.3.1.3 Plan after early termination of study

With 214 participants and a fixed maximum follow up period of 18months. Based on assumptions and monitoring of pooled event rates, we expect approximately 124 events to be observed at the time of the final analysis. 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), within 174 participants, and has 80% power to detect HR<0.59. The overall cohort, 214 patients, 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.

3.4 FRAMEWORK

3.4.1 Hypothesis testing framework

Alpha-spending approach to control primary analysis in the primary analysis population.

3.5 INTERIM ANALYSES AND STOPPING

A single interim analysis will be conducted after participants have at least 9 months follow up.

3.5.1 Initial planned interim analyses

A single interim analysis was to be conducted according to the alpha spending approach using an O'Brien-Fleming boundary. 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) who will also monitor selected safety endpoints, accrual and event rates.

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The interim analysis was to be conducted at least 6 months after the completion of recruitment and 50% of the information had been observed. The exact boundary was to be computed prior to the analysis according to the percentage of information observed. For example, at exactly 50% information (176 events) the analysis would have used alpha=0.0031 and declare a significant result if the observed HR<0.64. The final analysis (352 events) would be conducted with alpha=0.049 and have power of 85% if the HR=0.70.

3.5.1.1 Changes at time of Protocol V4

The interim analysis plan was unchanged in V4 apart from the lower number of expected events. The interim analysis was be conducted at least 6 months after the completion of recruitment AND at least 50% of the required information has been observed (156 events).

3.5.1.2 Plan after early termination of study V5

The interim analysis will be conducted after all participants have a minimum of 9 months follow up. This analysis will be prepared by the unblinded study statistician who will securely pass the results to the ISDMC.

3.5.2 Significance level adjustment

The interim analysis will be conducted with alpha=0.001. The remaining 0.049 will be apportioned to the primary analysis.

3.5.3 Guidelines for stopping

The study has completed recruitment prior to the interim analysis. If the interim analysis result is significant at the 0.001 level, the ISDMC will inform the TMC and the interim results will be made public.

3.6 TIMING OF FINAL ANALYSIS

3.6.1 Timing of final analysis

The primary analysis will be conducted after all patients have at least 18 months of follow-up.

3.7 TIMING OF OUTCOME ASSESSMENTS

3.7.1 Time points of measurement

Study assessments are conducted as follows:

- Screening (within 14 days prior to randomisation)
- Treatment (within 3 days prior to each treatment administration)
- End of treatment (4 weeks after end of treatment +/- 7 days)
- Until disease progression (6 weekly +/- 7 days)
- After disease progression (12 weekly +/- 14 days)

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3.7.1.1 Assessment details

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]

1. Participants will have their temperature, blood pressure, pulse rate and respiratory rate recorded as detailed in Section protocol 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.

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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. 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) **(c)** Baseline (Cycle 1 Day 1) **(d)** C1D15 (if on 2-weekly nivolumab) or C1D22 (if on 3-weekly nivolumab) **(e)** 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.

4 STATISTICAL PRINCIPLES

4.1 CONFIDENCE INTERVALS AND P VALUES

4.1.1 Level of statistical significance

The level of significance has been set at 5% type-one error.

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4.1.2 Adjustment for multiplicity

No formal adjustment will be made for multiplicity. All hypothesis tests undertaken will be reported for full transparency.

4.1.3 Confidence intervals

95% confidence intervals will be reported for all estimates.

4.2 ADHERENCE AND PROTOCOL DEVIATIONS

4.2.1 Adherence to the intervention

The compliance to treatment will be reported, including

4.2.2 Adherence presentation

Treatment regimens will be summarised separately

4.2.3 Protocol deviations for the trial

Protocol deviations will be categorised and grouped into into serious and inconsequential. Serious protocol deviations will be summarised with a summary of potential impact on interpretation.

4.3 ANALYSIS POPULATIONS

4.4 DEFINITION OF POPULATIONS

4.4.1.1 Primary analysis population

Primary analysis will be **chemotherapy control stratum** (includes participants randomly assigned to treatment with chemotherapy alone versus durvalumab plus chemotherapy). This is all patients who were recruited during protocol 1-3 and participants who were randomised into this stratum during protocol 4. This population will be defined according to the intention to treat principle.

4.4.1.2 Secondary analysis population

Secondary analysis will be all randomised participants as per intention to treat (i.e. randomised arm). This includes all participants protocols 1-4.

4.4.1.3 Tertiary analysis population

The immunotherapy control stratum (includes participants randomly assigned to treatment with immunotherapy alone versus durvalumab plus chemotherapy during protocol 4)

4.4.1.4 Treatment received populations

Similar populations will be constructed according to the treatment they received.

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5 TRIAL POPULATION

5.1 SCREENING DATA

5.1.1 Representativeness of sample

All people screened for entry into the DREAM3R study were recorded in the study database. A summary of the participation and reasons for non-participation will be included in the analysis report.

5.2 ELIGIBILITY

5.2.1 Summary of criteria

Adults commencing first-line systemic treatment for unresectable pleural mesothelioma; Epithelioid histology evaluable in all protocol versions, sarcomatoid and biphasic subtypes excluded following V4.

5.2.1.1 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, without prior radiotherapy to these sites.
3. Body weight >30kg.
4. ECOG performance status of 0 or 1.
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 109/L • Platelets ≥ 100 x 109/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.

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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 childbearing 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.

5.2.1.2 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.

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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.

5.3 RECRUITMENT

5.3.1 CONSORT flow diagram

The number of participants at each stage of the study will be included in a CONSORT diagram. Reasons for exclusion / withdrawal will be summarised at relevant stages. Key status times will be:

- enrolled
- randomised
- withdrawn
- treated
- progressed
- died

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5.4 WITHDRAWAL/FOLLOW-UP

5.4.1 Level of withdrawal

The number of participants who withdraw from the study (and reasons for their withdrawal) will be summarised.

5.4.2 Timing of data

Follow-up withdrawn participants will be performed at the time of interim & primary analysis.

5.4.3 How cases will be presented

Participants will be censored on date of withdrawal (or last known alive for overall survival).

5.5 BASELINE PATIENT CHARACTERISTICS

5.5.1 Characteristics summarised

All participant characteristics collected will be summarised by allocated treatment arm.

This includes: stratification factors, age, height, weight, body surface area, ethnicity, race, method of diagnosis, time since diagnosis, histology, t-stage (at diagnosis), n-stage, m-stage, prior radiotherapy, previous surgery, history of asbestos exposure, smoking history (and pack years). Blood biomarkers, patient reported quality of life. Age will be reported in categories (<50, 50-59, 60-69, 70-79, 80+).

5.5.2 How they will be described

- Continuous variables will be summarised with mean (SD), median, minimum and maximum.
- Categorical variables will be reported as n (%) for each level.

6 ANALYSIS

6.1 OUTCOME DEFINITIONS

Listing and details of the primary and all secondary outcomes.

6.1.1 Overall Survival (OS) - *Primary outcome*

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. Patients 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.

6.1.2 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

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1.1 for MPM and iRECIST (Protocol Sections 17.1 and 17.7). A patient who stops treatment with study drug and goes on to receive alternative therapy for MPM, prior to documentation of disease progression, will be considered to have progressed on that date. If a patient has not progressed or received alternative therapy, PFS will be censored on the date of the last disease assessment

6.1.3 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 malignant pleural mesothelioma (Protocol Section 17.1) and according to iRECIST (Protocol Sections 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.

6.1.4 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 (Protocol Section 17.6, Appendix 6).

6.1.5 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 to determine the effects durvalumab treatment has on participants QoL. The EORTC-recommended scoring guidelines will be used. A raw score will be 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 patient in any scale (e.g., symptoms, function, global health status) will be the threshold of a clinically meaningful change. 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.

6.1.6 Additional analyses

Additional analyses as outlined in the protocol will be conducted as part of the economic evaluation and exploratory translational research (reported separately).

6.2 ANALYSIS METHODS

6.2.1 Method used / presentation

All randomised patients will be included in the analysis. Except for safety data, all analyses will be conducted on an intention to treat basis (safety analysis will be reported by treatment as received within all patients who received any study treatment). 95% confidence intervals (CI) will be reported for all relevant estimates.

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The **primary endpoint** of the study is overall survival. All randomised patients 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.

Progression free survival (PFS) is a secondary endpoint of this study. All randomised patients will be included in the analysis of PFS. Results for PFS based on iRECIST will be considered exploratory.

OTRR will be conducted as per OS analysis plan. The primary estimate of ORR will be based on all patients randomised and compared using Cochran-Mantel-Hanzel test stratified by stratification factors. Results based on iRECIST will be considered exploratory.

Quality of life analysis will be conducted descriptively at each time point of collection. Trajectory of patient quality of life will be summarised. Time to deterioration in QOL will be analysed as per other time-to-event endpoints.

Exploratory analysis of biomarkers will be conducted and documented separately. In addition to exploratory analyses, PDL-1 expression status has been included as a planned subgroup. Tumour mutational burden (TMB) will also be included (once sensible cut points are determined). If no consensus is available prior to the final analysis, TMB will be split </≥ median value within the cohort.

6.2.2 Adjustment for covariates

In the primary analysis, the two treatment arms will be compared using the log-rank test stratified by stratification factors. Cox regression modelling will be used to estimate the treatment effect both on an unadjusted basis and adjusted for stratification variables. A multivariate cox model including stratification variables, ECOG and prior surgery will be reported. In the event of problems fitting the full model, a best subset approach will be taken to result in an optimal model.

The primary estimate of ORR will be based on all patients randomised and compared using Cochran-Mantel-Hanzel test stratified by stratification factors. Predictors of response will be evaluated using multivariate model variables.

Quality of life analysis will be conducted describing the trajectory of patient account for repeated measures.

6.2.3 Checking assumptions

There are no assumptions required for the primary analysis apart from non-informative censoring. Every effort will be made to ensure complete follow up information at the time of the primary analysis (including those patients who had withdrawn from study treatment).

Treatment estimates obtained from modelling approaches will be evaluated for suitability relative to their assumptions. E.g. proportion hazards assumption will be checked for Cox proportional hazards models.

6.2.4 Alternative methods

In the event of problems fitting the stratified log-rank test, modified test will be attempted. All tests undertaken will be reported along side the un-stratified test.

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6.2.5 Sensitivity analyses

The following sensitivity analyses are planned:

- For the PFS endpoint: A patient who stops treatment with study drug and goes on to receive alternative therapy for MPM, prior to documentation of disease progression, will be considered to be censored on that date.

6.2.6 Subgroup analyses

Planned subgroup analyses for study endpoints will be conducted for key factors used for stratification.

6.2.6.1 Subgroup definitions

1. Age (18-70 years vs. older than 70)
2. Sex (male vs. female)
3. Histology (epithelioid vs. non-epithelioid)
4. Region (Australia/New Zealand vs. USA)
5. Platinum Drug (cisplatin vs. carboplatin)
6. Planned control arm (chemotherapy vs. nivolumab+ipiluminnab)
7. PDL-1 status (<1%, 1%+)
8. Tumour mutational burden (grouping to be determined)

6.2.6.2 Planned subgroup analysis

Subgroup analyses will first test for evidence of interaction (using the treatment by subgroup term in the relevant Cox model). Then replicate the main analysis method for the overall population.

6.3 MISSING DATA

6.3.1 Assumptions / methods

No imputation of missing data is planned. The analysis approach incorporates information for each participant even if they are lost in follow-up. Information for key adjustment and subgroups will be complete as these variables were used for stratification of randomisation (completeness was a requirement of study entry).

For the response endpoint, the implicit assumption is that there no response unless observed otherwise.

6.4 ADDITIONAL ANALYSES

6.4.1 Additional statistical analyses

Additional analyses will be performed for tertiary endpoints and documented in separate SAPs as required.

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6.5 HARMS

6.5.1 Summarising safety data

All adverse events are recorded as per CTCAE. Frequency and severity of events observed will be summarised both as worst grade overall and by key categories. Adverse events of special interest will be summarised. All Serious Adverse Events (SAEs) will be summarised in more detail as appropriate.

6.6 STATISTICAL SOFTWARE

6.6.1 Packages used for analyses

R version R version 4.4.1 (2024-06-14), or later, will be used for analysis. All R packages (and versions) used will be documented as part of a reproducible analysis pipeline.

6.7 REFERENCES

6.7.1 Non-standard methods

Not applicable.

6.7.2 Data Management Plan

Standard operating procedures for the NHMRC Clinical Trials Centre (the coordinating centre) apply to all aspects of the study conduct.

6.7.3 Trial / Statistical Master File

All study documentation and analysis programs are stored in an electronic eTMF at the NHMRC Clinical Trials Centre. All analysis programs are version controlled.

6.7.4 Other documents

- DREAM3R study protocol publication: *Kok PS, Forde PM, Hughes B Thoracic Oncology Group of Australasia (TOGA) and PrECOG, USA, et al Protocol of DREAM3R: DuRvalumab with chEmotherapy as first-line treAtment in advanced pleural Mesothelioma—a phase 3 randomised trial BMJ Open 2022;12:e057663. doi: 10.1136/bmjopen-2021-057663*

- Results of CheckMate743: *Baas P. et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial, The Lancet, Volume 397, Issue 10272, 2021, Pages 375-386, ISSN 0140-6736, https://doi.org/10.1016/S0140-6736(20)32714-8.*

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