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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DREAM3R

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

Statistical Analysis Plan Amendment

[redacted] **- 2025-07-11**

Focus of amendment

This amendment was prepared to provide additional structure to the analysis in response to non-proportional hazards in the primary analysis endpoint.

Timeline of amendment

This amendment was prepared after the primary study statistician was unblinded to the results. The Australian study PIs reviewed the plan and provided input on the key aspects of the plan (methods and time for truncation / secondary times) whilst unblinded to the results. The second study statistician reviewed and approved the plan whilst still blinded to the results.

Summary of current plan

The current statistical analysis plan outlines the primary analysis as follows.

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.

6.2.1 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.

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.

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be made to ensure complete follow up information at the time of the primary analysis (including those patients who had withdrawn from study treatment).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 alongside the un-stratified test.

The plan didn't specify a fixed approach in response to non-proportional hazards.

Proposed additions

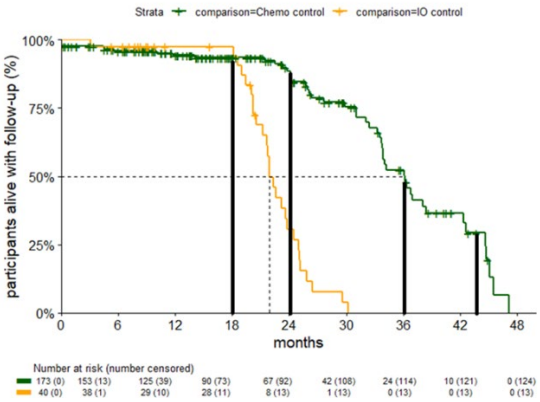
The planned analysis will be undertaken. The hazard ratio estimate will be plotted over time to aid visual understanding of changes. Additionally, time-to-event endpoints violating the non-proportional hazards assumption, will also be reported using Restricted Mean Survival Time (RMST). Estimates of HR partitioned into key time points will provide a secondary approach which may be easier to interpret than differences in RMST.

Detailed analysis plan

This plan was prepared after the data was finalised with minimum 18m follow-up on all participants. i.e. all event times and follow-up times were fixed. The primary cohort has mature follow-up relative to median survival (median follow-up = 36m, median pooled survival = 21m, survival estimate at median follow-up = 26%).

RMST is known to be sensitive to differential follow-up, uncertainty in estimates in the tail of Kaplan-Meier curves[1]. We propose the primary truncation of time for RMST analysis in primary cohort to use the median follow-up time within that cohort (36 m). Secondary estimates will be produced at the "minimum of maximum observed event time" (rounded to 42m) and the cohort "minimum follow-up time" (24m). Similar periods will be constructed for other cohorts.

Hazard will be estimated across three distinct time periods (0-12m, 12-24m and 24+) to represent chemotherapy, maintenance durvalumab and post study treatment periods. If needed, similar periods will be used for progression free survival (0-6m, 6-12m, 18+).



[1] Lu Tian et al., 'On the Empirical Choice of the Time Window for Restricted Mean Survival Time', *Biometrics* 76, no. 4 (December 2020): 1157–66, https://doi.org/10.1111/biom.13237.