CONFIRM

Statistical Analysis Plan

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To be approved and reviewed by:

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List of Abbreviations

Abbreviation		Abbreviation	
AACR	American Association of Cancer Research	MHRA	Medicines and Healthcare products Regulatory Agency
AE	Adverse Event	NCI	National Cancer Institute
ALT	Alanine aminotransferase	NHS IC	National Health Service Identification Centre
AR	Adverse Reaction	NSCLC	Non-small cell lung cancer
AST	Aspartate aminotransferase	ORR	Objective response rate
BMS	Bristol-Myers Squibb	PR	Partial response
BP	Blood pressure	Q2W	Every two weeks
BUN	Blood urea nitrogen	REC	Research Ethics Committee
CI	Chief Investigator	RR	Respiratory rate
CRF	Case Report Form	SAE	Serious Adverse Event
CTA	Clinical Trial Authorisation	SAP	Statistical Analysis Plan
CTCAE	Common Terminology Criteria for Adverse Events	SAR	Serious Adverse Reaction
DMP	Data Management Plan	SCNA	Somatic copy number alteration
ECOG	Eastern Cooperative Oncology Group	SCTU	Southampton Clinical Trials Unit
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels	SUSAR	Suspected Unexpected Serious Adverse Reaction
FFPE	Formalin-fixed, paraffin-embedded	TMF	Trial Master File
GCP	Good Clinical Practice	TMG	Trial Management Group
HR	Hazard Ratio	TSC	Trial Steering Committee
IASLC	International Association for the Study of Lung Cancer	TSH	Thyroid-stimulating hormone
IB	Investigator's Brochure	T3	Triiodothyronine
IDMC	Independent data monitoring committee	T4	Thyroxine
IMP	Investigational Medicinal Product	UAR	Unexpected Adverse Reaction
ISF	Investigator Site File	ULN	Upper limits of normal
LDH	Lactate dehydrogenase	WOCBP	Women of childbearing potential

Keywords

Mesothelioma; anti PD-1; Nivolumab; immunotherapy; RECIST; quality of life; survival; immune checkpoint inhibition; PD-L1

1 Introduction

1.1 Purpose of SAP

This statistical analysis plan (SAP) describes in detail the methods that will be used to analyse the data collected as part of the CONFIRM trial. This will form the basis of the final trial publication. The final analysis will follow the SAP to ensure that the analyses are conducted in a scientifically valid manner and to avoid, or clearly identify, post-hoc decisions that may affect the interpretation of the statistical analysis. Any deviations from the SAP will be detailed in the final report.

This SAP is based on CONFIRM SAP v1.0 that was produced for the purposes of the preliminary publication, following the recommendations of the Data Monitoring and Ethics Committee (DMEC), as ratified by the Trial Steering Committee (TSC) (see v1.0 "Purpose of SAP" for further details) to release early, interim results. This SAP will follow the version numbering of the preliminary publication SAP, so that changes from the preliminary analysis are logged in the SAP revision history in a transparent manner.

A Health Economics Analysis Plan will be developed separately to this SAP.

1.2 Trial Personnel

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1.3 Trial background and rationale (short synopsis)

Effective therapy for relapsed mesothelioma is an unmet need. Despite a significant number of clinical studies in the second line setting, no randomised study to date has been positive. The James Lind Alliance Priority Setting Partnership funded by the NIHR has identified immunotherapy as the number one UK research priority. To date there have been no placebo controlled randomised trials for mesothelioma using PD-L1 or PD-1 checkpoint inhibition.

Early promising signals of activity relating to both PD-L1 and PD-1 targeted treatment in mesothelioma implicate a dependency of mesothelioma on this immune checkpoint, and support the development of a randomised phase III trial to evaluate the efficacy of nivolumab. CONFIRM will be the first ever placebo controlled, randomised phase III trial of a PD-1 immune checkpoint inhibitor.

PD-1 checkpoint inhibition has revolutionised the treatment of melanoma and is now standard of care in non-small cell lung cancer, squamous cell cancer head and neck and classical Hodgkin's lymphoma. It is being assessed rigorously in numerous other cancers making its evaluation in mesothelioma timely in CONFIRM.

1.4 Objectives

Primary objectives:

- To compare overall survival (OS) of nivolumab with placebo in patients with relapsed mesothelioma (co-primary endpoint)
- To compare progression-free survival (PFS) of nivolumab with placebo, as determined by investigator (PFSi; co-primary endpoint)

Secondary objectives:

- To compare objective response rate (ORR), as determined by investigator, of nivolumab to placebo
- To compare progression-free survival (PFS), of nivolumab to placebo, based on mRECIST and RECIST1.1 (PFSr)
- To determine the safety profile of nivolumab in relapsed mesothelioma patients

Translational objectives:

- To define the association of PD-L1 status with PFS and OS in patients with relapsed mesothelioma
- To correlate:
  a) Mutation burden with OS
  b) Immunosuppressive landscape (immune checkpoint expression and infiltration of immune cell) and nivolumab efficacy

1.5 Definition of endpoints

1.5.1 Definition of primary endpoint

Overall survival and progression-free survival (investigator reported) are co-primary endpoints.

Overall survival is defined as time from randomisation to death from any cause.

Progression-free survival (investigator reported) is defined as time from randomisation to progression (according to investigator reported progression), or death from any cause (whichever event comes first).

1.5.2 Definition of secondary endpoints

- **Progression-free survival** (based on mRECIST and RECIST1.1) is defined as time from randomisation to progression (according to modified RECIST or RECIST 1.1 of target lesion, assessment/appearance of non-target lesion), or death from any cause (whichever event comes first).

- **Objective response rate** (based on mRECIST and RECIST 1.1) is defined as the proportion of people who have complete or partial response while on treatment. (Note that this deviates from the protocol, which specifies investigator reported objective response rate; however, the database is only designed to collect investigator reported progression, rather than response. Hence, mRECIST and RECIST 1.1 will be used to determine response rate.)

N.B. mRECIST or RECIST 1.1 will be assessed at week 6 (±3 days) and week 12 (±3 days) (regardless of the number of cycles of treatment the patient has received and whether trial treatment has stopped early for reasons other than progression).

- **Toxicity** will be assessed using CTCAE v4.03 at baseline, after each treatment cycle, and for 100 days post treatment discontinuation and for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible.
- Treatment compliance will be assessed by early stopping of treatment, dose delays, and interruptions.

The remaining endpoints (EQ-5D and cost-effectiveness) will be described in a separate health economics analysis plan.

1.5.3 Definition of translational endpoints

PD-L1 expression will be determined by immunohistochemistry and subgroup analysis based on:

- Negative (<1%), low positive (1-49%), high positive (≥50%)
- Negative (<1%), positive (≥1%)

will assess the predictive value of PD-L1 for the co-primary endpoints of overall survival and progression-free survival (investigator reported).

An analysis plan for the remaining translational endpoints (tumour immune cell infiltration, mutation/copy number burden, neoantigen burden, immune escape, HLA loss of heterozygosity and somatic driver alterations) will be developed separate to this SAP.

1.6 Analysis principles

All analyses will be reported according to CONSORT (2010) and Southampton Clinical Trials Unit (SCTU) standard operating procedure (SOP) on planning, implementing and reporting statistical analyses (CTU/SOP/5058).

2 Design considerations

2.1 Description of trial design

A double blind, placebo controlled randomised phase III trial comparing nivolumab (anti PD-1 antibody) monotherapy 240mg every two weeks versus placebo. The treatment allocation ratio will be 2:1 in favour of nivolumab.

Patients will receive treatment with nivolumab at a dose of 240mg (or placebo) as a 30-minute IV infusion, on Day 1 (±2) of every 14-day treatment cycle, until progression, unacceptable toxicity, withdrawal of consent, or the maximum treatment duration of 12 months is reached, whichever occurs first. There will be no dose escalations or reductions of IMP allowed. Patients may be dosed no less than 12 days from the previous dose.

2.2 Trial power and sample size

The original sample size calculation was based on overall survival (OS) only (see full details below). This calculation accounted for a number of interim analyses (efficacy and futility) by using an alpha of 0.04 for the sample size (and ultimately the interpretation). During the course of the trial, the independent Trial Steering Committee (TSC) approved the inclusion of progression-free survival (PFS) as a co-primary endpoint in order to mitigate against the risk of treatment cross-over impacting the trial results, on the condition of maintaining the original sample size for OS. The analysis was planned to follow the Fallback procedure [25], though no explicit correction or acknowledgement of the impact of the analysis (where alpha is split across the endpoints) on sample size was initially proposed.

Following a later review by the TSC (meeting date 13th January 2020), all future interim analyses (which were formal rule-based efficacy and futility analyses) were removed; this decision was taken for three reasons: 1) a subset of the interim analyses were based on the PD-L1 positive subgroup, but analyses based on this could not take place until after recruitment was complete (due to delays in collecting samples and processing the results), lessening the potential benefit of carrying out these analyses; 2) the percentage of the samples that were PD-L1 positive was lower than anticipated at the start of the trial (due to changes in how the analysis is carried out using an approved 22C3 antibody assay - meaning a greater number of patients would need to be recruited to obtain a sufficient number who were PD-L1 +ve to conduct the analysis); and 3) the futility analyses would also not take place until very near the end (or after) the recruitment phase had completed. Due to 1) and 2) above it was not possible to undertake the PD-L1 +ve analysis during the recruitment period of the trials and as there was also little benefit in being able to stop the study for futility after the recruitment period, the TSC were keen to allow the study to run to completion. (Note: one analysis for harm had been carried out prior to this meeting, which was not relevant for the original sample size calculation.)

It was agreed that removing the formal interim analyses and accounting for the Fallback procedure in the final analysis would have no net effect on the sample size calculation, meaning the original sample size calculations hold. Although the original sample size calculation accounted for interim analyses that have been subsequently removed, the Fallback procedure was not originally accounted for. The result is that an alpha of 0.04 is to be used for the analysis of OS (as originally proposed), and, according to the Fallback procedure, an alpha for PFS of 0.05 (if OS null hypothesis is rejected) or 0.01 (if OS null hypothesis is not rejected). This approach maintains an overall 5% type 1 error rate across the co-primary endpoints, and will serve the purpose of demonstrating a treatment effect on either OS or PFS that is sufficient to establish clinical benefit; i.e., if the analysis of OS shows a statistically significant effect (at 0.04) this will be sufficient to establish clinical benefit (irrespective of whether PFS is statistically significant or not), but

if OS is non-significant, clinical benefit may still be established if PFS is statistically significant (at remaining unused alpha level of 0.01).

The independent data monitoring committee (IDMC) met on 13th August 2020 and recommended early release of the PFS and OS results, subsequently ratified by the TSC (who were unblinded at this point on order to review the relevant IDMC reports). It was agreed between the TMG and TSC that investigator reported PFS would be an appropriate definition of PFS, given that the study was blinded and that this was more likely to reflect clinical decision-making (e.g., stopping of treatment). This principle is maintained for this final analysis, where investigator reported PFS is considered the co-primary outcome.

2.2.1 Power calculation for Overall Survival

Based on the VANTAGE trial [20] the expected median survival of patients on placebo is approximately 6 months.

Sample size assumptions (using artsurv in Stata): Based on a hazard ratio of 0.70 (equivalent to extending the median overall survival rate from 6 months to 8.5 months, or increasing the 6 months overall survival rate from 50% to 61.5% - considered a clinically significant difference by the research team); 80% power; recruitment period of 4 years, then 6 months follow-up period; 2-sided significance level of 4% (based on Fallback procedure); negligible drop out. Number of patients required: 336 (224 in the experimental arm and 112 in the control arm), a total of 291 events (deaths).

2.2.2 Power calculation for Progression Free Survival

Based on the DETERMINE trial [24] the expected median PFS of patients on placebo is approximately 3 months.

The original sample size of 336 patients will also provide 80% power to detect a hazard ratio of 0.65 (equivalent to extending the median PFS from 3 months to 4.6 months or increasing the 3-month PFS rate from 50% to 63.7% - considered a clinically significant difference by the research team); with recruitment period of 4 years; 6 months follow-up period; 2-sided significance level of 1% (remaining unused alpha from Fallback procedure for 5% level overall); negligible drop out. This will require a total of 284 events (progression or deaths) (calculated using artsurv in Stata).

2.3 Randomisation details

Patients will be randomised to either nivolumab or the control arm on a 2:1 allocation. Patients will be stratified according to histology (epithelioid versus non-epithelioid).

2.4 Timing of planned analyses

2.4.1 Interim analyses and early stopping

As per protocol v8, there are no planned stopping guidelines for this trial.

2.4.2 Preliminary data analysis

The independent data monitoring committee (IDMC) met on 13th August 2020 and recommended early release of the progression free survival (PFS) and overall survival (OS) results; this was later ratified by the Trial Steering Committee (TSC). The use of investigator reported PFS (i.e., not independently confirmed PFS, through review of RECIST measures) was agreed by the Trial Management Group (TMG), and the TSC chair and statistician, to be a meaningful measure of PFS, and should form the basis of the early PFS results given the incomplete RECIST data at the time. It was agreed by the IDMC and TSC that OS results could be released even if had not reached its required number events.

2.4.3 Final data analysis

Final analysis is planned to coincide with reaching 291 deaths (as per the sample size calculation in protocol v8).

3 Statistical considerations

3.1 Definition of analysis populations

3.1.1 Intention-to-treat analysis population

This population consists of all patients who have consented and been randomised to a treatment arm. All summaries and analyses will be on the ITT population unless otherwise specified.

3.1.2 Safety analysis population

This population consists of the ITT population who have received at least one dose of treatment.

3.2 Analysis software

All analyses will be carried out using STATA v16 or higher and/or SAS v9.4 or higher.

3.3 Methods for handling data

3.3.1 Withdrawal from trial

All data up until the point of patient withdrawal from the trial will be used in analyses unless the patient withdrew consent and does not wish for the data already collected prior to withdrawal to be used for the trial.

3.3.2 Missing data

The default position is that no imputation of missing or incomplete data is planned for the primary or secondary analyses, as the co-primary endpoints of PFS and OS are expected to largely be complete. Even following trial withdrawal, participants can contribute to OS and PFS analyses (as the time on trial until withdrawal can be used). Reasons for trial withdrawal will be presented descriptively to allow for any assessment of informative withdrawal, which may affect the interpretation of the results.

3.3.3 Outliers

There is no method planned for the handling of outliers in the data for the primary or secondary analyses.

3.3.4 Assumption checking and alternative methods

The proportional hazards assumptions underlying the Cox regression models described will be checked by plotting the log cumulative hazard against log time, which will yield roughly parallel lines for each study arm should the proportional hazards assumption be valid. Schoenfeld residuals will also be examined.

If the proportional hazards assumption does not appear to hold, other statistical methods will be explored, e.g., time-varying Cox model (e.g., piecewise model) and/or flexible parametric model.

3.3.5 Data transformations

There are no data transformations planned for this study.

3.4 Definition of key derived variables

3.4.1 Time since historical diagnosis of mesothelioma

Time in months from the date of historical diagnosis of mesothelioma to the date of the baseline visit.

3.4.2 Progression-free survival - investigator reported (PFSi)

PFSi is defined as time from randomisation to progression (according to investigator reported progression), or death from any cause. Those alive with no investigator reported progression will be censored at the time last seen (or spoken to, if a COVID-19 telephone consultation took place).

3.4.3 Overall Survival (OS)

Overall survival is defined as time from randomisation to death from any cause. Those alive will be censored at the time last seen (or spoken to if a COVID-19 telephone consultation took place).

3.4.4 Progression-free survival – RECIST (PFSr) and overall response rate

PFSr is defined as the time from randomisation to progression, as defined by mRECIST and RECIST 1.1 (referred to collectively as RECIST from hereon), or death from any cause. Those alive with no RECIST-defined progression will be censored at time last seen. The derivation of RECIST will follow that of Byrne & Novak (2004; mRECIST) and Eisenhauer et al. (2009; RECIST 1.1), as described below.

The mRECIST guidelines provide a basis for dealing with measures taken on the pleura. Up to six measures, consisting of no more than two measures taken across three sites, are used to determine tumour thickness perpendicular to the chest wall or mediastinum. Summed together, these provide a single unidimensional measurement to be incorporated in the RECIST 1.1 measurement process. As per RECIST 1.1 criteria, a further four target lesions may be identified to represent measurable (target) lesions (representing five in total, with no more than two from a single organ (where the pleura counts as a single organ). Measures from a target lesion are unidimensional and are summed for a total score for target lesions. Further measurable lesions, and non-measurable lesions, are assessed as non-target lesions. (Note, it is possible that a participant does not have measures taken on the pleura, and so RECIST measures are based on RECIST 1.1 alone.)

At follow-up scans, the response category of an individual is determined by combining information on target lesions, non-target lesions, and new lesions. For target lesions, the following criteria are set:

Response category for target lesions	**Criteria**
Complete response	Disappearance of all target lesions
Partial response	≥30% decrease in sum of measures compared to baseline
Progressive disease	≥20% increase from nadir (i.e., not necessarily baseline, if lesions previously shrunk compared to baseline)
Stable disease	Not meeting other criteria

Non-target lesions are assessed according to the following criteria:

Response category for non-target lesions	**Criteria**
Complete response (CR)	Disappearance of all non-target lesions
Progressive disease (PD)	Unequivocal progression of existing non-target lesions
Non CR/non-PD	Persistence of one or more non-target lesions

Lastly, the appearance of new lesions is counted as progressive disease.

Target, non-target, and new lesions information is combined to an overall RECIST category. If any of target, non-target or new lesions are classified as progressive disease, then the overall classification will be progressive disease; otherwise, the below table summarises the classification:

Target lesion category	Non-target lesion category	New lesions	Overall RECIST category
Complete response	Complete response	No	Complete response
Complete response	Non-CR/non-PD or not all evaluated	No	Partial response
Partial response	*Not PD (including if not all evaluated)*	No	Partial response
Stable disease	*Not PD (including if not all evaluated)*	No	Stable disease

Each follow-up scan contributes a response category for an individual. Overall response rate is the proportion of participants who have either complete or partial response as their best response. Best response is taken to be the best response category while on treatment, based on the (best to worst) ordering of: complete response, partial response, stable disease, progressive disease.

3.5 General principles for reporting and analysis

The following principles should be applied:

- A 2-sided 95% confidence interval (CI) will be presented for the primary analysis of the primary endpoint, alongside p-values. The co-primary endpoints will be assessed under the Fallback procedure, designed to control overall type 1 error rate. A difference in OS will be considered statistically significant for $p \leq 0.04$. Dependent on the result for OS, PFSi will be considered statistically significant at either $p \leq 0.01$ (if OS not statistically significant) or $p \leq 0.05$ (if OS is statistically significant).
- For all other analyses, 2-sided 95% CIs, p-values, and 5% significance level will be applied, unless otherwise stated.
- There will be no adjustments for multiplicity, besides those applied through the Fallback procedure for the co-primary endpoints.
- Descriptive statistics will be presented as appropriate to the nature of the data. For example, continuous variables will usually be summarised by the number of observations, mean and standard deviation (or median and IQR if the data appears skewed/not normal), minimum, and maximum. Categorical variables may be summarised by frequency counts and percentages for each category.
- Unless otherwise stated, percentages will be presented to one decimal place.
- For continuous data, the mean, standard deviation, median and quartiles will be rounded to one additional decimal place compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.
- Unless otherwise stated, baseline data will be defined as the last available recorded measurement prior to administration of the first treatment on cycle 1 day 1.
- The labelling of the study arms will be as follows:
    - Nivolumab for the Nivolumab treatment group
    - Placebo for the Placebo treatment group
- In the case of partial dates, the RAVE imputed date will be used (1st Month/Jan).

4 Planned analyses and reporting

4.1 Disposition of the study population

Patient disposition will be summarised in a CONSORT flow diagram, showing a clear account of all patients who entered the study. These will be based on the enrolled population and will include:

- The number of patients assessed for eligibility and reason for not randomising
- The start and stop date of recruitment
- The number of patients randomised to each study arm
- The number of patients in the ITT population
- The number of patients in the safety population (who received at least one dose of study medication)
- The reasons for end of study
- Duration of follow-up (median and 95% CI follow-up obtained from reversing the OS endpoint, where death counts as being censored)

The disposition and treatment information above will also be summarised, along with the following:

- Stratification factors
    - The number of patients in each arm with epithelioid vs non-epithelioid mesothelioma
- Subgroup populations
    - The number of patients in each arm by PD-L1 status

4.2 Protocol deviations and unblinding summary

Any major Corrective And Preventative Actions (CAPAs) reported to the SCTU will be listed. Unblindings will be summarised by arm, alongside reasons, reported as frequencies and percentages.

4.3 Post-study therapy

Treatment received post-study will be summarised by arm, focusing on chemotherapy and immunotherapy, reported as frequencies and percentages.

4.4 Baseline characteristics

- Age
- Sex
- ECOG performance status
- Histology (epithelioid versus non-epithelioid)
- Asbestos exposure (yes/no)
- Smoking status
- Time since histological diagnosis of mesothelioma
- Stage
- Extra-thoracic metastases
- Site of mesothelioma (pleural or non-pleural)
- Line of treatment

4.5 Treatment Information

- Total duration of treatment received (minutes)
- Dose delay
- Dose interruptions
- Number of days on treatment

4.6 Primary endpoints

4.6.1 Overall Survival (OS)

OS is one of two co-primary endpoints in this trial, and the first in the hierarchy to be tested according to the Fallback procedure used in the study. Analysis will be based on the ITT population. The potential for participants to become unblinded (usually after progression) with the aim of seeking further treatment beyond the trial is classed an intercurrent event, according to the ICH E9 addendum on estimands and sensitivity analysis. Using the ITT population is equivalent to the treatment policy strategy, as defined by this addendum. The impact of control arm participants accessing immunotherapy off-study is partly handled by the inclusion of progression-free survival as a co-primary outcome. Early stopping of treatment (for other reasons besides progression), dose delays and interruptions will also be handled according to the treatment policy strategy.

The co-primary analysis will be based on OS compared between study arms using a Cox proportional hazards regression model adjusted for the stratification factor (epithelioid vs. non-epithelioid) and line of therapy. The p-value associated with study arm will be determined from this model together with the estimated hazard ratio and associated 95% 2-sided confidence interval. If the observed OS difference in favour of Nivolumab (based on the hazard ratio) is statistically significant at the 2-sided 4% level, this will be considered a signal of clinical benefit.

OS will also be presented graphically using a Kaplan-Meier (K-M) plot, with survival curves for each arm. In addition, the median OS and 12-month OS survival probabilities, and associated 95% CI, will be obtained. A reverse K-M will be applied to obtain the median maturity follow-up (if <60% of participants have reached the OS endpoint).

The proportional hazards model assumption will be evaluated, as described in section 3.3.4. The use of parametric models (e.g., Weibull) will be considered if there is evidence of non-proportional hazards.

The primary analysis will be repeated with an interaction term for PD-L1 status, to assess if the positive group are more likely to respond to treatment. This model will include PD-L1 status as a main effect.

Finally, a forest plot will be presented, with estimated hazard ratios (95% confidence intervals) and p-values for OS across the following variables:

- Age (<75 years, or 75 years and older)
- Sex
- Asbestos exposure
- Histology (epithelioid or non-epithelioid)
- Line of therapy
- Smoking status
- Site of mesothelioma
- Extra-thoracic metastases
- ECOG

- PD-L1 status (high positive, low positive, negative)
- LDH (split at the median)
- Neutrophil/lymphocyte ratio (split at the median)

4.6.2 Progression-Free Survival (PFS) - investigator reported

PFSi is the second co-primary endpoint according to the hierarchy of the Fallback procedure used in the study. It will be analysed according to the ITT principle. Non-adherence to treatment (early stopping, delays) may be an intercurrent event, but the treatment policy strategy is the targeted estimand.

The co-primary analysis will be based on PFSi compared between study arms, using a Cox regression model adjusted stratification factor (epithelioid vs. non-epithelioid) and line of therapy. The p-value associated with study arm will be determined from this model together with the estimated hazard ratio and associated 95% 2-sided confidence interval. Analysis will follow the Fallback procedure, where the level used to judge statistical significance for PFS will depend on the result for OS. OS will be judged at an alpha of 0.04, and PFSi will be 0.05 or 0.01 depending on the statistical significance or not, respectively, of OS. If the observed PFSi difference in favour of Nivolumab (based on the hazard ratio) is statistically significant at the appropriate level based on the OS result, this will be a signal of clinical benefit.

PFS will also be presented graphically using Kaplan-Meier plots. In addition, the median PFS and 12-month PFS survival probabilities, and associated 95% CI, will be obtained. A reverse K-M will be applied to obtain the median maturity follow-up (if <60% of participants have reached the PFSi endpoint).

The proportional hazards model assumption will be evaluated, as described in section 2.7.4. The use of parametric models (e.g., Weibull) will be considered if there is evidence of non-proportional hazards.

The primary analysis will be repeated with an interaction term for PD-L1 status, to assess if the positive group are more likely to respond to treatment. This model will include PD-L1 status as a main effect.

Finally, a forest plot will be presented, with the same information as specified for OS in section 4.6.1.

4.7 Secondary endpoints

- Response rate – determined by complete response or partial response while on treatment, according to mRECIST and RECIST 1.1; frequencies and percentages will be reported with corresponding 95% CIs for the latter, based on the Wilson Score method.
- Progression-free survival based on mRECIST and RECIST1.1. This will be analysed the same as PFS (investigator reported) above, without p-value thresholds. This will be supported by a waterfall plot (a histogram of best response per person, according to percentage change in RECIST measurements from baseline) and a spider plot (line graph of RECIST measurements over time, per person) for the Nivolumab arm.
- Landmark analyses:
    - OS will be further analysed using 6-week and 12-week landmarks. For the Nivolumab arm, two groups will be formed according to whether a patient has progressed or not (according to investigator reported definition) by the landmark time. Anyone who has died or withdrawn prior to the landmark time will be excluded. Median OS and survival at one year after the landmark will be presented alongside the respective 95% confidence intervals. Progression will be assessed using the 6- or 12-week scan data as recorded in the database in the 6- or 12-week folder, rather than using an exact cut-off of 6 or 12 weeks.
    - The above analysis will be repeated for OS according to RECIST categories of partial or complete response, stable disease, and progressive disease.

- Treatment compliance: cycles and duration of treatment will be summarised based on the information available in the Nivolumab/Placebo administration forms, first date of treatment and last dose information. The start of treatment is defined as cycle 1 when the first dose is administrated. End of treatment information will be summarised as:
    - Number of patients who received at least one dose (Nivolumab/Placebo)
    - Discontinued Nivolumab/Placebo and reason for discontinuation

  Treatment duration will be summarised as follows:
    - The total number of cycles received
    - The median duration of treatment of Nivolumab or placebo (cycle 1 day 1 to last dose, inclusive)
    - Number of patients who had at least one Nivolumab /Placebo dose reduction
    - Number of patients who had at least one Nivolumab/Placebo dose missed

4.7.1 Quality of Life and Health Economic data

Health economics analysis will be described in a separate analysis plan.

4.8 Translational endpoints

The co-primary analyses will be repeated with the addition of PD-L1 status in two ways (1: positive [1+%] or negative [<1%]; 2: high positive [50+%], low positive [1-49%] and negative [<1%]). The role of PD-L1 status will be explored through the use of an interaction with treatment term in the Cox models.

Further translational analyses will be described in a separate analysis plan.

4.9 Safety reporting

All safety analyses will be performed on the safety population unless otherwise stated. Further summaries other than those described below (e.g., AEs leading to discontinuations, AE's leading to deaths, AE causality or other displays) may be reported at the discretion of the CI, following review.

4.9.1 Adverse events

Overall toxicity will be summarised by arm using frequencies and percentages. This will involve summarising the worst grade experienced by participants, the number of participants experiencing at least one AE, and the number of participants experiencing an AE by preferred terms and system organ class according to MedDRA coding.

4.9.2 Severe Adverse Events

For each study arm, the number of patients that experienced at least one AE graded 3 or above will be summarised overall, by system organ class (SOC) and preferred term. Patients with any AE graded 5 will be noted in the footnote of the table.

4.9.3 Serious Adverse Events

Serious toxicity includes serious adverse events (SAEs), serious adverse reactions (SARs) and suspected unexpected serious adverse reactions (SUSARs). In this section the term "serious adverse events (SAEs)" encompasses SAEs, SARs, SUSARs.

The total number of SAEs, the number of patients that experienced at least one SAE and the number of SAEs per patient (for patients experiencing at least one SAE, median and range) will be presented by study arm. The PI assessment, the number of SAEs by CTCAE grade and the reason for their seriousness will be presented for all SAEs by study arm.

The number of patients with at least one SAE will be summarised by system organ class (SOC) and preferred term for each study arm. This table will also be presented for SAEs grade 3 and above.

5 Tables, listings and figures templates

5.1 List of tables, figures, and listings

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5.2 Patient disposition

Figure 1 CONSORT flow diagram of patient disposition

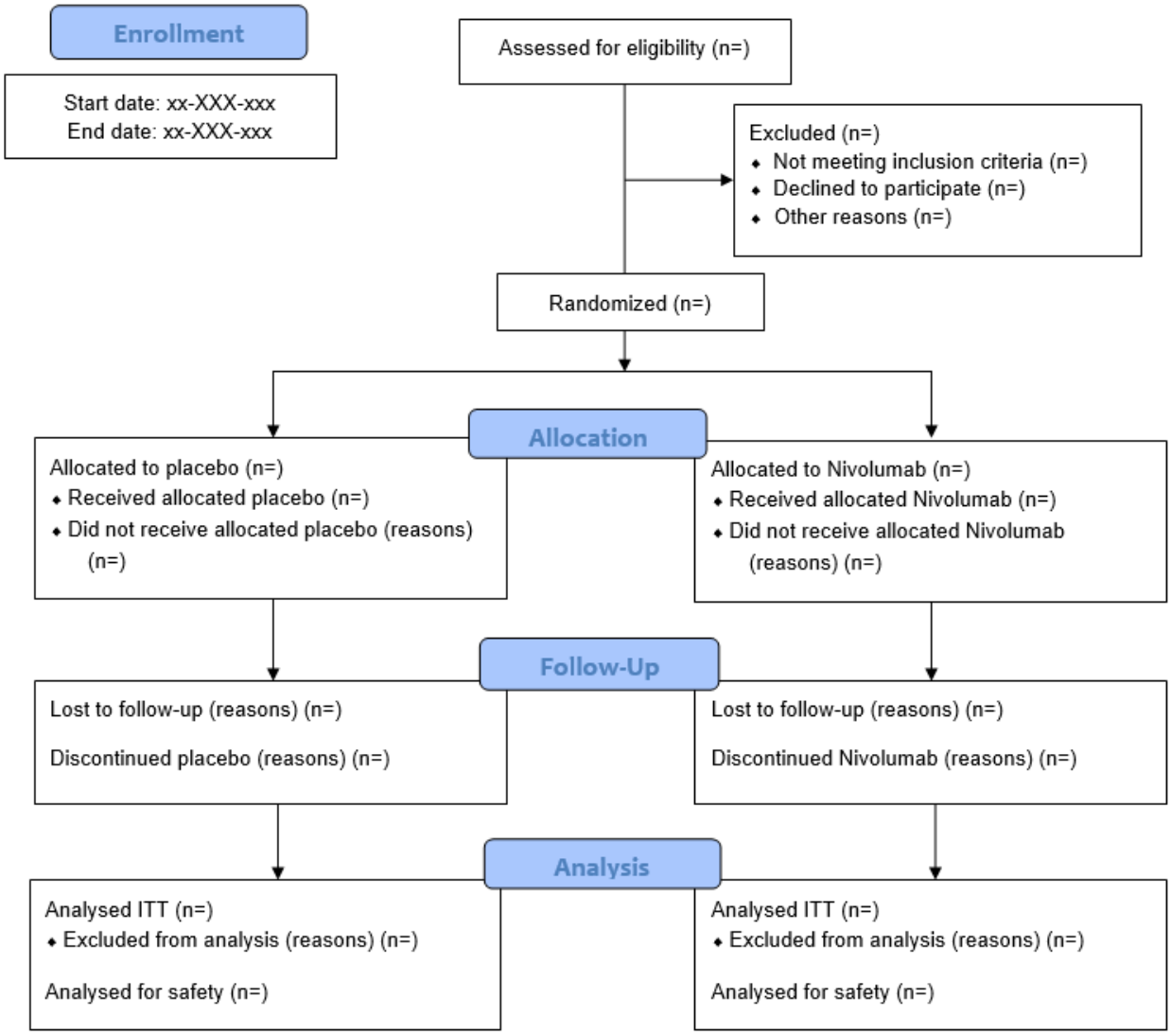


Table 1 End of Study information form the End of Study form

End of Study	Nivolumab (n=xx)	Placebo (n=xx)	Total (n=xx)
Primary reason for end of study			
Completed[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Lost to follow-up	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Physician's decision	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Withdrawal by subject	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc.			

Note: Percentages are based on the number of patients per arm

[1]Still alive at end of trial when no further data collection is to be undertaken

5.3 Protocol deviations and unblinding

Table 2 Major protocol violations (excluding occurrences of unblinding)

Violation	Patient/site affected (if applicable)	Comments	Actions

Programming note: this information will come from the trial management team.

Table 3 Unblindings summary (by arm)

Characteristic	Nivolumab (n=xxx)	Placebo (n=xxx)	Total (n=xxx)
No. of patients unblinded – n(%)[1]	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
Reason for unblinding – n(%)[2]			
Consideration for further treatment	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Consideration for another trial	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Emergency Unblinding	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
For PV Team - for SAE Reporting	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Patients request	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Progression	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] Denominator is the number of patients randomised.
[2] Denominator is the number of patients randomised and who were unblinded.

Table 4 Post-study Therapy from the Post-Study Therapy form

Characteristic	Nivolumab (n=xxx)	Placebo (n=xxx)	Total (n=xxx)
No. of patients with any further treatment – n(%)[1]	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
Type of further treatment – n(%)[2]			
Platinum-based therapy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pemetrexed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Immunotherapy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Nivolumab	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Radiotherapy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] Denominator is the number of patients randomised.
[2] Denominator is the number of patients who received further treatment; patients can receive more than one type of therapy and so percentages will not sum to 100.

5.4 Demographic and baseline characteristics

Table 5 Demographic information recorded at baseline

Characteristic	Nivolumab (n=xxx)	Placebo (n=xxx)	Total (n=xxx)
Age (years)			
Median	xx.x	xx.x	xx.x
Quartiles	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Range	xx to xx	xx to xx	xx to xx
Missing from eCRF	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Sex – n(%)			
Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Undifferentiated	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
ECOG – n(%)			
0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PD-L1 Status – n(%)			
Highly positive (≥50%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Positive (1-49%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
All positive (≥1%)	*xx (xx.x%)*	*xx (xx.x%)*	*xx (xx.x%)*
Negative (<1%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Could not be measured	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Asbestos Exposure – n(%)			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Smoking Status – n(%)			
No Smoker	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Ex-Smoker	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Time since diagnosis of mesothelioma (months)			
Median	xxx.x	xxx.x	xxx.x
Quartiles	xxx.x, xxx.x	xxx.x, xxx.x	xxx.x, xxx.x
Range	xxx.x to xxx.x	xxx.x to xxx.x	xxx.x to xxx.x
Missing from eCRF	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 6 Disease characteristics from the Disease Characteristics and Medical History form

Characteristic	Nivolumab (n=xxx)	Placebo (n=xxx)	Total (n=xxx)
Histology – n(%)			
Epithelioid	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-epithelioid	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Site of mesothelioma – n(%)			
Pleural	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-pleural	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Extra-thoracic metastases – n(%)			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
TNM staging			
T stage – n(%)			
T0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
T1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
T2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
T3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
T4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
N stage – n(%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
N0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
N1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
N2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
N3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
M stage – n(%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
M0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
M1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Line of treatment – n(%)			
2nd line	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3rd line	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Greater than 3rd line	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

5.5 Treatment information

Table 7 Treatment Information from Drug Exposure form

Characteristic	Nivolumab (n=xxx)	Placebo (n=xxx)	Total (n=xxx)
Total duration of treatment received (minutes)			
Median	xxx.x	xxx.x	xxx.x
Quartiles	xxx to xxx	xxx to xxx	xxx to xxx
Missing from CRF – n(%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of days on treatment[1]			
Median	xx.x	xx.x	xx.x
Quartiles	xxx to xxx	xxx to xxx	xxx to xxx
Range	xxx to xxx	xxx to xxx	xxx to xxx
Missing from CRF – n(%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of cycles			
Median	xx.x	xx.x	xx.x
Quartiles	xxx to xxx	xxx to xxx	xxx to xxx
Range	xxx to xxx	xxx to xxx	xxx to xxx
Any dose delay – n(%)			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from CRF – n(%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Any dose interruption – n(%)			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from CRF – n(%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1]Defined as the date of last infusion minus date of first infusion + 1

5.6 Primary Endpoint Analysis

5.6.1 Overall Survival Information

Table 8 Overall survival information, including Cox models

Characteristic	Nivolumab (n=xxx)	Placebo (n=xxx)	Total (n=xxx)
Median follow-up – median (95%CI)	xx (xx to xx)	xx (xx to xx)	xx (xx to xx)
Number of events observed – n(%)	xx (xx%)	xx (xx%)	xx (xx%)
Median overall survival – median (95% CI)	xx (xx to xx)	xx (xx to xx)	xx (xx to xx)

Characteristic	Nivolumab (n=xxx)	Placebo (n=xxx)	Total (n=xxx)
12-month overall survival – % (95% CI)	xx% (xx% to xx%)	xx% (xx% to xx%)	xx% (xx% to xx%)
Cox's proportional hazards model[1] – unadjusted			
P-value		xx	
Hazard Ratio (95% CI)		xx (xx to xx)	
Cox's proportional hazards model[1,2] – adjusted			
P-value		xx	
Hazard Ratio (95% CI)		xx (xx to xx)	

[1]Reference category=Placebo:

- A HR<1 favours Nivolumab
- A HR=1 indicates neither favoured.
- A HR>1 favours Placebo

[2]Adjusting for epithelioid vs. non-epithelioid

Overall survival is deemed significant if the p-value is ≤0.04, as per the Fallback procedure.

Figure 2 **Kaplan-Meier plot for overall survivial by treatment arm**

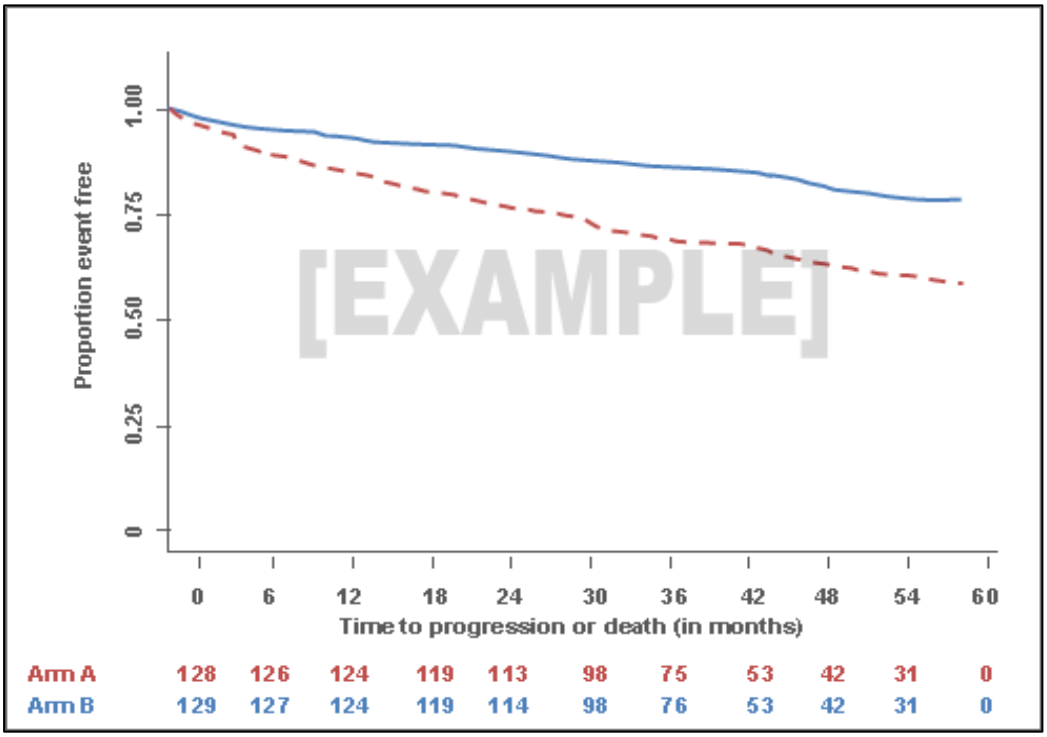


Figure 3 Log cumulative hazard versus time (OS)

Figure 4 Schoenfeld residuals (OS)

5.6.2 Progression-Free Survival Information

Table 9 Progression-free survival (investigator reported) information, including Cox models

Characteristic	Nivolumab (n=xxx)	Placebo (n=xxx)	Total (n=xxx)
Number of events observed – n(%)	xx (xx%)	xx (xx%)	xx (xx%)
Median progression free survival – median (95% CI)	xx (xx to xx)	xx (xx to xx)	xx (xx to xx)
12-month progression free survival – % (95% CI)	xx% (xx% to xx%)	xx% (xx% to xx%)	xx% (xx% to xx%)
Cox's proportional hazards model[1] – unadjusted			
P-value		xx	
Hazard Ratio (95% CI)		xx (xx, xx)	
Cox's proportional hazards model[1,2] – adjusted			
P-value		xx	
Hazard Ratio (95% CI)		xx (xx, xx)	

[1]Reference category=Placebo:

- A HR<1 favours Nivolumab
- A HR=1 indicates neither favoured.
- A HR>1 favours Placebo

[2]Adjusting for epithelioid vs. non-epithelioid

Progression free survival is deemed significant if the p-value is ≤0.01 (if OS is not significant) or ≤0.05 (if OS is significant), as per the Fallback procedure.

Figure 5 Kaplan-Meier plot for progresion free survivial (investigator reported) by treatment arm

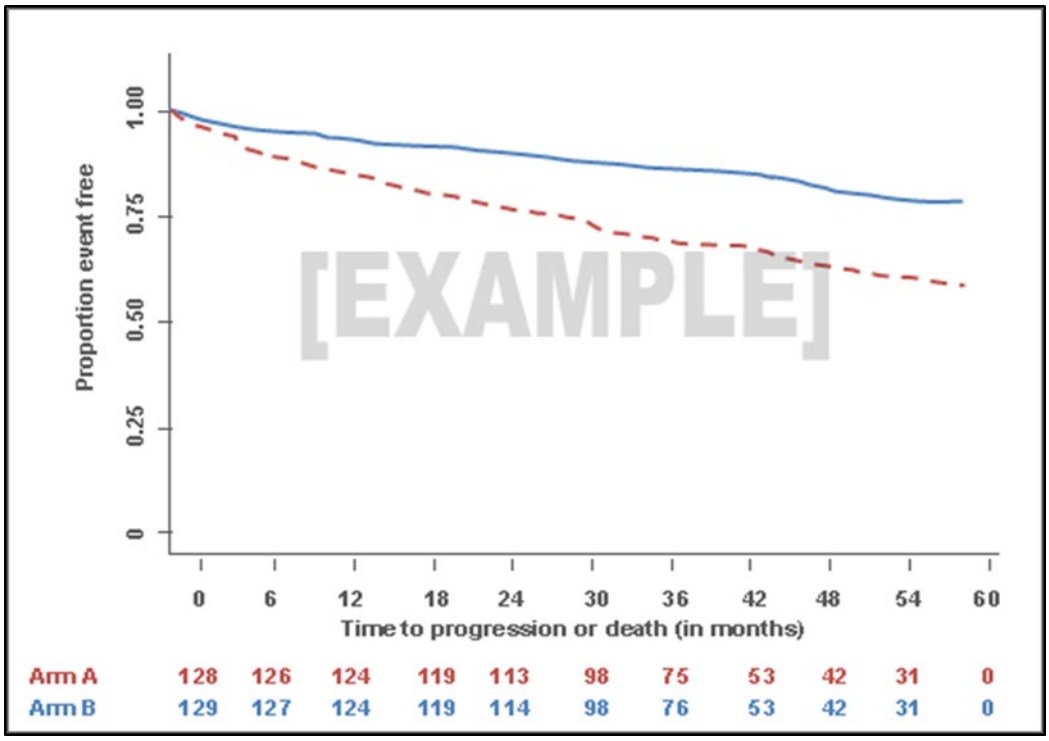


Figure 6 Log cumulative hazard versus time (PFS)

Figure 7 Schoenfeld residuals (PFS)

5.7 Secondary Endpoint Analysis

5.7.1 RECIST-derived endpoints

Table 10 Progression-free survival (determined by RECIST) information, including Cox models

Characteristic	Nivolumab (n=xx)	Placebo (n=xx)	Total (n=xx)
Number of events observed – n(%)	xx (xx%)	xx (xx%)	xx (xx%)
Median progression free survival – median (95% CI)	xx (xx to xx)	xx (xx to xx)	xx (xx to xx)
12-month progression free survival – % (95% CI)	xx% (xx% to xx%)	xx% (xx% to xx%)	xx% (xx% to xx%)
Cox's proportional hazards model[1] – unadjusted			
P-value		xx	
Hazard Ratio (95% CI)		xx (xx, xx)	
Cox's proportional hazards model[1,2] – adjusted			
P-value		xx	
Hazard Ratio (95% CI)		xx (xx, xx)	

[1] Reference category=Placebo:

- A HR<1 favours Nivolumab
- A HR=1 indicates neither favoured.
- A HR>1 favours Placebo

[2] Adjusting for epithelioid vs. non-epithelioid

Figure 4 Kaplan-Meier plot for progresion free survivial (determined by RECIST) by treatment arm

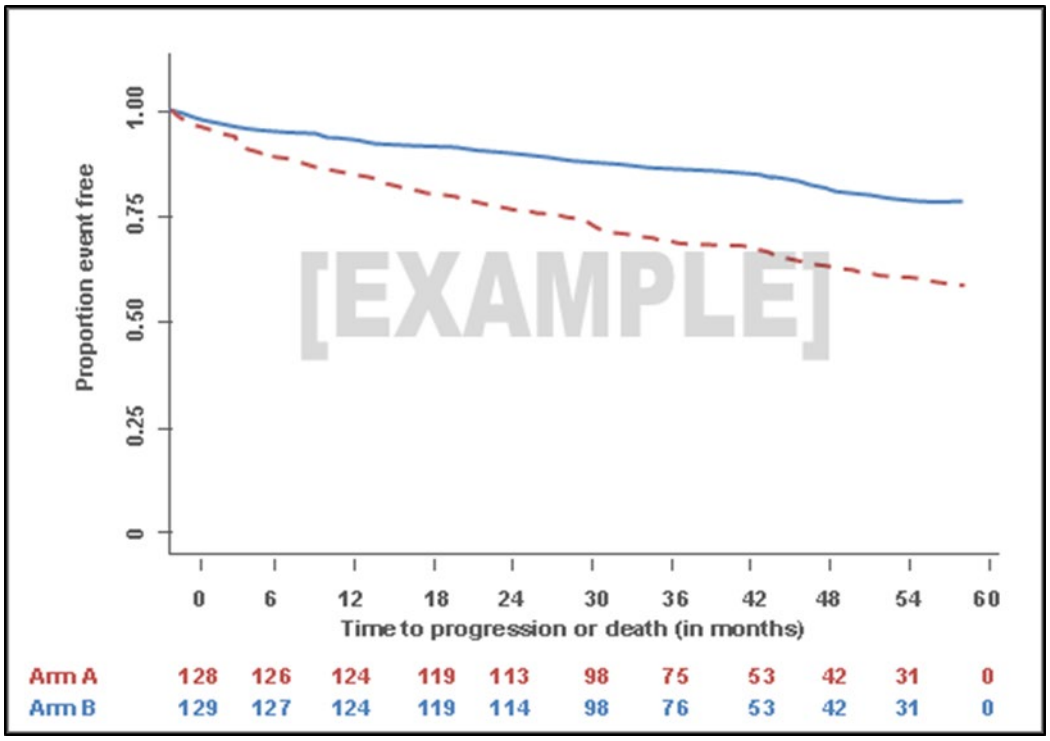


Table 11 Progression data by arm

Characteristic	Nivolumab (n=xx)	Placebo (n=xx)	Total (n=xx)
Best overall response on treatment			
Complete response	xx (xx%)	xx (xx%)	xx (xx%)
Partial response	xx (xx%)	xx (xx%)	xx (xx%)
Stable disease	xx (xx%)	xx (xx%)	xx (xx%)
Progression	xx (xx%)	xx (xx%)	xx (xx%)

Figure 8 Waterfall plot of percentage change in RECIST measurements for the Nivolumab arm

This plot illustrates the per patient best percentage change in the size of the sum of the target lesions from the baseline scan until end of treatment, for the Nivolumab arm only. Patients are ordered from largest increase to largest decrease in size, with colour coding according to RECIST categorisation.

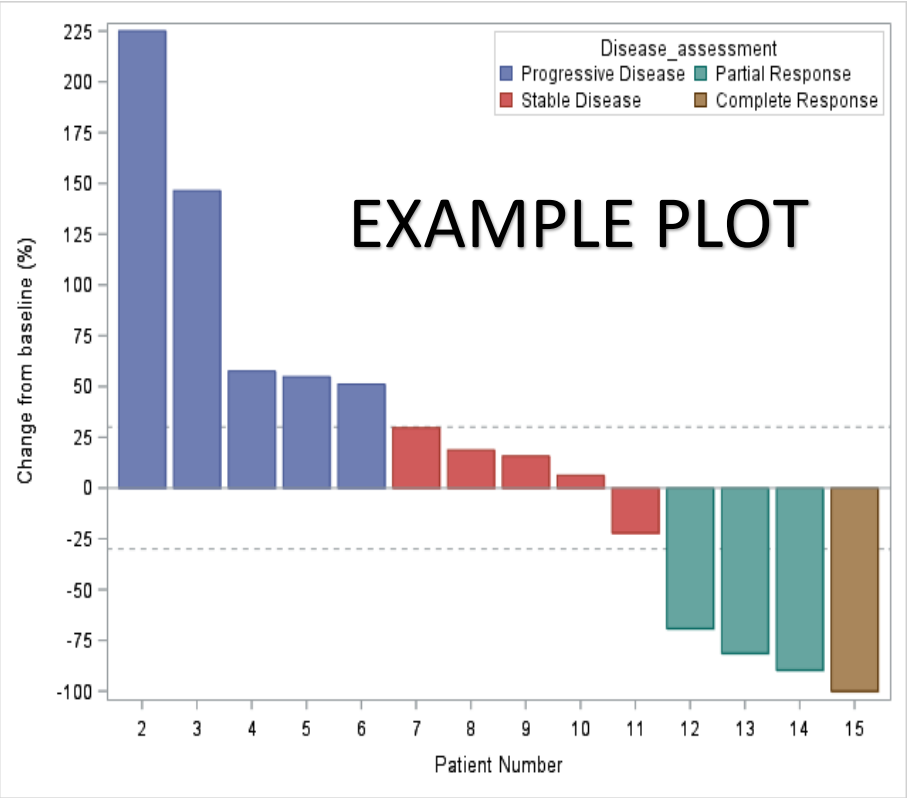
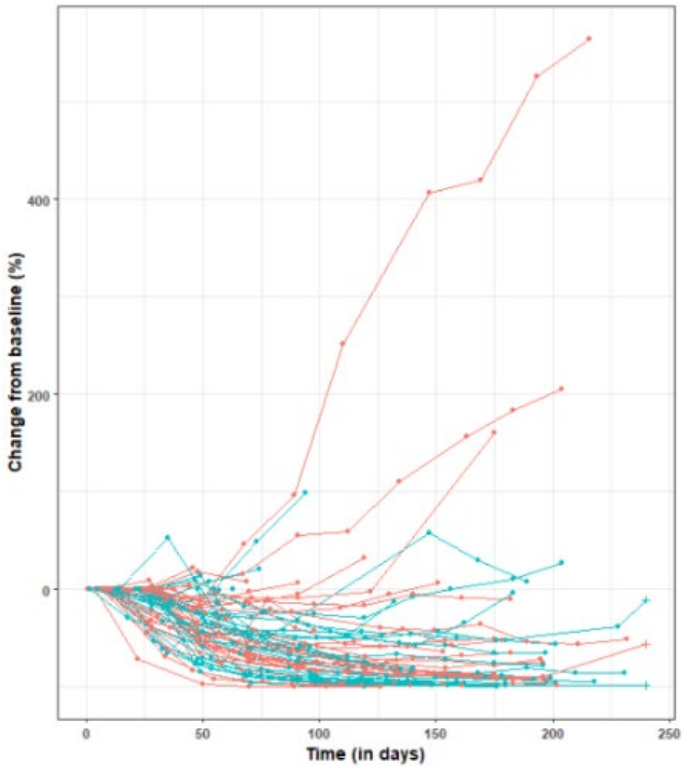


Figure 9 Spider plot of change from baseline in RECIST measurements

This plot illustrates the percentage change in the size of the sum of the target lesions from the baseline scan for all scans until end of treatment, with one line per patient. Group is colour coded.



5.7.2 Time to response and duration of response

Table 12 Time to response

Characteristic	Nivolumab (n=xxx)	Placebo (n=xxx)
Number of patients responded[1] – n(%)	xx (xx%)	xx (xx%)
Time to response (months)[2] – median (IQR)	xx (xx to xx)	xx (xx to xx)

[1]Response is defined by complete response (CR) or partial response (PR).
[2]Defined by time from randomisation to response.

Table 13 Duration of response

Characteristic	Nivolumab (n=xxx)	Placebo (n=xxx)
Number of patients responded[1] – n(%)	xx (xx%)	xx (xx%)
Number of patients progressed/died – n(%)[2]	xx (xx%)	xx (xx%)
Duration of response[3] (months) – median (IQR)	xx (xx to xx)	xx (xx to xx)

[1]Response is defined by complete response (CR) or partial response (PR).
[2] Denominator is the number of patients who had a response.
[3]Defined by time from response to disease progression/death, patients who haven't progressed/died will be censored at the LKA date.

5.7.3 Landmark analyses

Table 14 Overall survival information for the Nivolumab arm using a landmark of 6 weeks

Characteristic	Nivolumab arm only (n=xxx)[1]	
	Responders (n=xxx)	Non-responders (n=xxx)
Number of events observed – n(%)	xx (xx%)	xx (xx%)
Median overall survival – median (95% CI)	xx (xx to xx)	xx (xx to xx)
12-month[2] overall survival – % (95% CI)	xx% (xx% to xx%)	xx% (xx% to xx%)

[1]Represents the number of patients who had not died or withdrawn before their 6-week scan
[2]Timing from the date of a patients' 6-week scan.

Table 15 Overall survival information for the Nivolumab arm using a landmark of 12 weeks

Characteristic	Nivolumab arm only (n=xxx)[1]	
	Responders (n=xxx)	Non-responders (n=xxx)
Number of events observed – n(%)	xx (xx%)	xx (xx%)
Median overall survival – median (95% CI)	xx (xx to xx)	xx (xx to xx)
12-month[2] overall survival – % (95% CI)	xx% (xx% to xx%)	xx% (xx% to xx%)

[1]Represents the number of patients who had not died or withdrawn before their 12-week scan
[2]Timing from the date of a patients' 12-week scan

5.8 Biomarker subgroup Analysis

5.8.1 Overall Survival Information

Table 16 Overall survival information for the PD-L1 subgroup, including Cox models

Characteristic	Nivolumab (n=xxx)		Placebo (n=xxx)		Total (n=xxx)	
	PD-L1 +ve (n=xxx)	PD-L1 -ve (n=xxx)	PD-L1 +ve (n=xxx)	PD-L1 -ve (n=xxx)	PD-L1 +ve (n=xxx)	PD-L1 -ve (n=xxx)
Number of events observed – n(%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Median overall survival – median (95% CI)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
12 month overall survival – % (95% CI)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)

Cox's proportional hazards model including treatment and PD-L1 status interaction[1, 2, 3] – adjusted

Treatment

P-value	x.xxx
Hazard Ratio (95% CI)	x.xxx (x.xxx, x.xxx)

PD-L1 status

P-value	x.xxx
Hazard Ratio (95% CI)	x.xxx (x.xxx, x.xxx)

Treatment*PD-L1 status

P-value	x.xxx
Hazard Ratio (95% CI)	x.xxx (x.xxx, x.xxx)

[1] Reference category=Placebo

[2] Reference category=Negative PD-L1 status

[3] Adjusted for epithelioid status and line of treatment

Table 17 Overall survival information for the PD-L1 subgroup, including Cox models

Characteristic	Nivolumab (n=xxx)			Placebo (n=xxx)			Total (n=xxx)		
	PD-L1 high +ve (n=xxx)	**PD-L1 low +ve (n=xxx)**	**PD-L1 -ve (n=xxx)**	**PD-L1 high +ve (n=xxx)**	**PD-L1 low +ve (n=xxx)**	**PD-L1 -ve (n=xxx)**	**PD-L1 high +ve (n=xxx)**	**PD-L1 low +ve (n=xxx)**	**PD-L1 -ve (n=xxx)**
Number of events observed – n(%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Median overall survival – median (95% CI)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
12 month overall survival – % (95% CI)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)

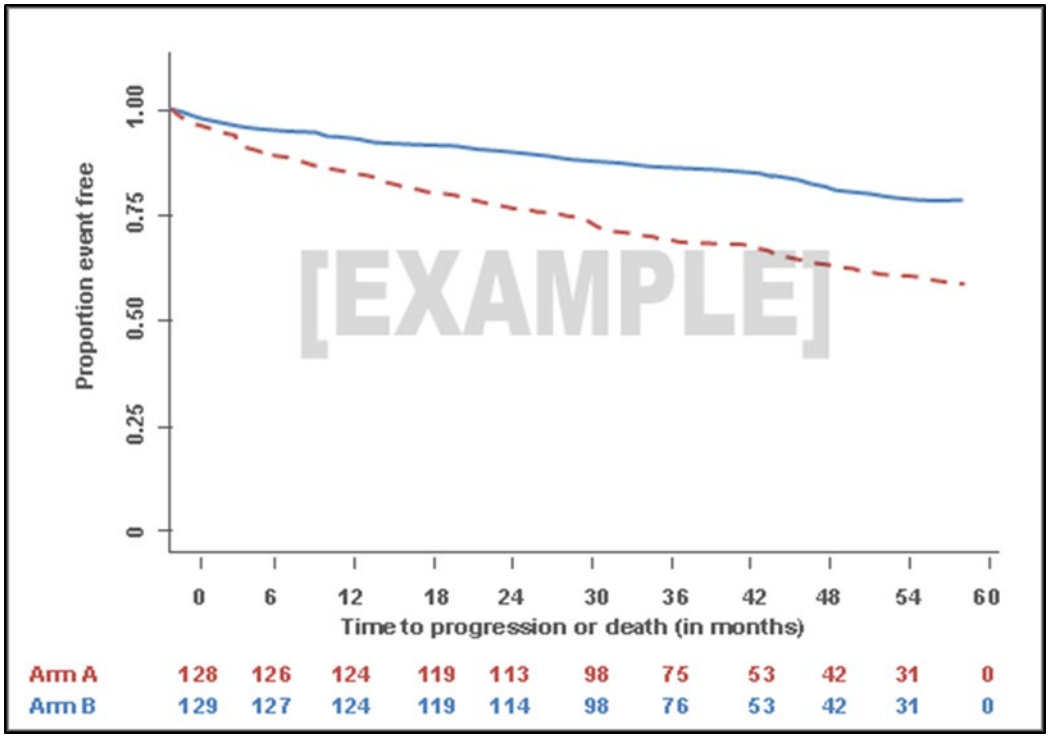
Cox's proportional hazards model including treatment and PD-L1 status interaction[1, 2, 3] – adjusted	
Treatment	
P-value	x.xxx
Hazard Ratio (95% CI)	x.xxx (x.xxx, x.xxx)
PD-L1 high +ve	
P-value	x.xxx
Hazard Ratio (95% CI)	x.xxx (x.xxx, x.xxx)
PD-L1 low +ve	
P-value	x.xxx
Hazard Ratio (95% CI)	x.xxx (x.xxx, x.xxx)
Treatment*PD-L1 high +ve	
P-value	x.xxx
Hazard Ratio (95% CI)	x.xxx (x.xxx, x.xxx)
Treatment*PD-L1 low +ve	
P-value	x.xxx
Hazard Ratio (95% CI)	x.xxx (x.xxx, x.xxx)

[1] Reference category=Placebo

[2] Reference category=Negative PD-L1 status

[3] Adjusted for epithelioid status and line of treatment

Figure 10 Kaplan-Meier plot for overall survivial by treatment arm and PD-L1 status



5.8.2 Progression Free Survival Information

Table 18 Progression free survival (investigator reported) information for the PD-L1 subgroup, including Cox models

Characteristic	Nivolumab (n=xxx)		Placebo (n=xxx)		Total (n=xxx)	
	PD-L1 +ve (n=xxx)	PD-L1 -ve (n=xxx)	PD-L1 +ve (n=xxx)	PD-L1 -ve (n=xxx)	PD-L1 +ve (n=xxx)	PD-L1 -ve (n=xxx)
Number of events observed – n(%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Median overall survival – median (95% CI)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
12 month overall survival – % (95% CI)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)

Cox's proportional hazards model including treatment and PD-L1 status interaction[1, 2, 3] – adjusted

Treatment	
P-value	x.xxx
Hazard Ratio (95% CI)	x.xxx (x.xxx, x.xxx)
PD-L1 status	
P-value	x.xxx
Hazard Ratio (95% CI)	x.xxx (x.xxx, x.xxx)
Treatment*PD-L1 status	
P-value	x.xxx
Hazard Ratio (95% CI)	x.xxx (x.xxx, x.xxx)

[1] Reference category=Placebo

[2] Reference category=Negative PD-L1 status

[3] Adjusted for epithelioid status and line of treatment

Table 19 Progression free survival (investigator reported) information for the PD-L1 subgroup, including Cox models

Characteristic	Nivolumab (n=xxx)			Placebo (n=xxx)			Total (n=xxx)		
	PD-L1 high +ve (n=xxx)	**PD-L1 low +ve (n=xxx)**	**PD-L1 -ve (n=xxx)**	**PD-L1 high +ve (n=xxx)**	**PD-L1 low +ve (n=xxx)**	**PD-L1 -ve (n=xxx)**	**PD-L1 high +ve (n=xxx)**	**PD-L1 low +ve (n=xxx)**	**PD-L1 -ve (n=xxx)**
Number of events observed – n(%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Median overall survival – median (95% CI)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
12 month overall survival – % (95% CI)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)

Cox's proportional hazards model including treatment and PD-L1 status interaction[1, 2, 3] – adjusted	
Treatment	
P-value	x.xxx
Hazard Ratio (95% CI)	x.xxx (x.xxx, x.xxx)
PD-L1 high +ve	
P-value	x.xxx
Hazard Ratio (95% CI)	x.xxx (x.xxx, x.xxx)
PD-L1 low +ve	
P-value	x.xxx
Hazard Ratio (95% CI)	x.xxx (x.xxx, x.xxx)
Treatment*PD-L1 high +ve	
P-value	x.xxx
Hazard Ratio (95% CI)	x.xxx (x.xxx, x.xxx)
Treatment*PD-L1 low +ve	
P-value	x.xxx
Hazard Ratio (95% CI)	x.xxx (x.xxx, x.xxx)

[1] Reference category=Placebo

[2] Reference category=Negative PD-L1 status

[3] Adjusted for epithelioid status and line of treatment

Figure 11 Kaplan-Meier plot for progression free survivial by treatment arm and PD-L1 status

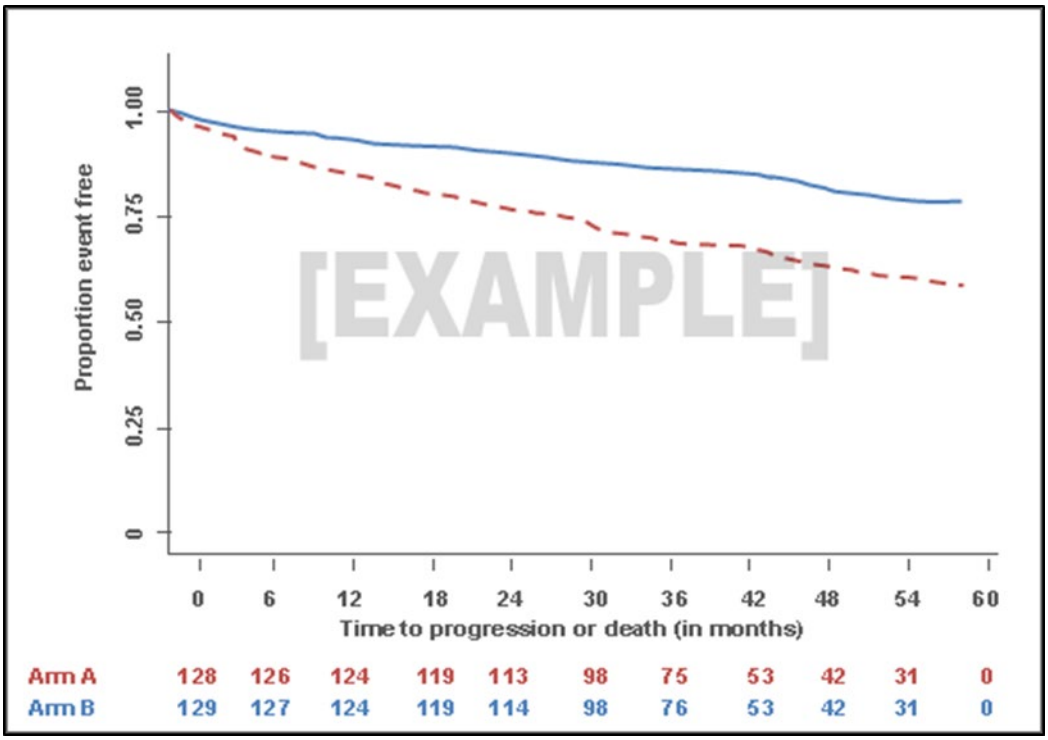


Table 20 Progression (according to mRECIST and RECIST 1.1) data by arm

Characteristic	Nivolumab		Placebo		Total	
	PD-L1 +ve (n=xx)	PD-L1 -ve (n=xx)	PD-L1 +ve (n=xx)	PD-L1 -ve (n=xx)	PD-L1 +ve (n=xx)	PD-L1 -ve (n=xx)
Best overall response[1]						
Complete response	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Partial response	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Stable disease	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Progression	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

[1]Investigator response

Figure 6 Forest plot

A forest plot will be used to display treatment effect (based on hazard ratios and confidence intervals from univariable Cox proportional hazards model) across the following variables:

- Age (<75 years, or 75 years and older)
- Sex
- Asbestos exposure
- Histology (epithelioid or non-epithelioid)
- Line of therapy
- Smoking status

- Site of mesothelioma
- Extra-thoracic metastases
- ECOG
- PD-L1 status (high positive, low positive, negative)
- LDH (split at the median)
- Neutrophil/lymphocyte ratio (split at the median)

5.9 Safety reporting

5.9.1 Toxicity

Table 21 Overall toxicity by CTCAE Grade

Characteristic	Nivolumab (n=xxx)	Placebo (n=xxx)	Total (n=xxx)
Adverse events – n(%)[1,2]			
CTCAE 4.0 Grade 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE 4.0 Grade 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE 4.0 Grade 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE 4.0 Grade 4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE 4.0 Grade 5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reported AE with Missing Grade – n(%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No AE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe (CTCAE v4.0 Grade 3 or above) adverse events – n(%)[1,2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] Denominator is the number of patients randomised.
[2] The worst grade is used when more than one grade is available for a patient.

Table 22 Overall Toxicity

Characteristic	Nivolumab (n=xxx)	Placebo (n=xxx)	Total (n=xxx)
Number of patients experiencing at least one AE – n(%)[1]	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
Summary of AEs – n(%)[1, 2]			
Blood and lymphatic system disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
… [*]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cardiac disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Ear and labyrinth disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Endocrine disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Eye disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Gastrointestinal disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

General disorders and administration site conditions	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Hepatobiliary disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Immune system disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Infections and infestations	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Injury, poisoning and procedural complications	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Investigations	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Metabolism and nutrition disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Musculoskeletal and connective tissue disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Nervous system disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Psychiatric disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Renal and urinary disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reproductive system and breast disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Respiratory, thoracic and mediastinal disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Skin and subcutaneous tissue disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Surgical and medical procedures	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Vascular disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] Denominator is the number of patients randomised.
[2] The worst grade is used when more than one grade is available for a patient.
[*] This data will be preferred terms within the system organ class.

Table 23 Overall Toxicity (Grade 3 or above)

Characteristic	Nivolumab (n=xxx)	Placebo (n=xxx)	Total (n=xxx)
Number of patients that experienced at least one grade 3 or above AE – n(%)[1]	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
Summary of AEs – n(%)[1, 2]			
Blood and lymphatic system disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cardiac disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Ear and labyrinth disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Endocrine disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Eye disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Gastrointestinal disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
General disorders and administration site conditions	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Hepatobiliary disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Immune system disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Infections and infestations	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Injury, poisoning and procedural complications	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**

…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Investigations	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Metabolism and nutrition disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Musculoskeletal and connective tissue disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Nervous system disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Psychiatric disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Renal and urinary disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reproductive system and breast disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Respiratory, thoracic and mediastinal disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Skin and subcutaneous tissue disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Surgical and medical procedures	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Vascular disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] Denominator is the number of patients randomised.

[2] The worst grade is used when more than one grade is available for a patient.

5.9.2 Reported Serious Adverse Events (SAEs)/Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

There have been xxx SAEs/SARs/SUSARs reported. A summary of these are shown below together with a full list of each event reported sorted by Principal Investigator (PI) assessment, patient and date.

Table 24 Summary of the SAEs reported

Characteristic	Nivolumab (n=xxx)	Placebo (n=xxx)	Total (n=xxx)
Number of patients experiencing at least one SAE/SAR/SUSAR – n(%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of SAE/SAR/SUSAR per patient (for patients with at least one SAE/SAR/SUSAR) – median (range)	x (x.x to x.x)	x (x.x to x.x)	x (x.x to x.x)
Overall assessment – n(%)[2]			
SUSAR (Suspected Unexpected Serious Adverse Reaction)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SAR (Serious Adverse Reaction)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SAE (Serious Adverse Event)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pending SUSAR	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE v4.0 grade – n(%)[2]			
1 – Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2 – Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3 – Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4 – Life threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5 – Death related to AE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Why was the event serious – n(%)[3]			
1 – Resulted in death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2 – Life threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3 – Required hospitalisation or prolongation of existing hospitalisation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
6 – Other important medical event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] Denominator is the number of patients randomised.

[2] Denominator is the number of SAEs/SARs/SUSARs with non-missing information. Overall assessment relates to worst case based on PI and independent, blinded clinical review.

[3] Denominator is the number of SAEs/SARs/SUSAR.

Table 25 Summary of the main symptom(s) reported on the SAE form

Characteristic	Nivolumab (n=xxx)	Placebo (n=xxx)	Total (n=xxx)
Number of patients experiencing at least one SAE/SAR/SUSAR – n(%)[1]	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
Summary of SAEs – n(%)[1, 2]			
Blood and lymphatic system disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cardiac disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Endocrine disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Eye disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Gastrointestinal disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
General disorders and administration site conditions	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Hepatobiliary disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Infections and infestations	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Injury, poisoning and procedural complications	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Investigations	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Metabolism and nutrition disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Musculoskeletal and connective tissue disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Nervous system disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Psychiatric disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Renal and urinary disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reproductive system and breast disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Respiratory, thoracic and mediastinal disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Surgical and medical procedures	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Vascular Disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] Denominator is the number of patients randomised.

[2] The worst grade is used when more than one grade is available for a patient

Table 26 Summary of the main symptom(s) reported on the SAE form (Grade 3 or above)

Characteristic	Nivolumab (n=xxx)	Placebo (n=xxx)	Total (n=xxx)
Number of patients that experienced at least one grade 3 or above SAE – n(%)[1]	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
Summary of SAEs – n(%)[1, 2]			
Blood and lymphatic system disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cardiac disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Endocrine disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Eye disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Gastrointestinal disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
General disorders and administration site conditions	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Hepatobiliary disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Infections and infestations	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Injury, poisoning and procedural complications	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Investigations	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Metabolism and nutrition disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Musculoskeletal and connective tissue disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Nervous system disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Psychiatric disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Renal and urinary disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reproductive system and breast disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Respiratory, thoracic and mediastinal disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Surgical and medical procedures	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Vascular Disorders	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] Denominator is the number of patients randomised.

[2] The worst grade is used when more than one grade is available for a patient**.**

References

Byrne & Novak (2004). Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. *Annals of Oncology*. Vol. 15: 257-260. DOI: 10.1093/annonc/mdh059

Eisenhauer *et al.* (2009). New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *European Journal of Cancer*. Vol. 45: 228-247

6 SAP revision history

Version number	Revision history	Author	Date
0.1	First draft – based on v7 of the protocol	Sam Wilding	07-SEP-2020
0.2	Updates following review by Kayleigh Hill	Kayleigh Hill	08-OCT-2020
0.3	Updated following review by Gareth Griffiths and Dean Fennell	Kayleigh Hill	25-OCT-2020
1.0	Updated following review by Sean Ewings and Dean Fennell This version was used for the preliminary analysis (see v1.0 for full explanation).	Sean Ewings	26-OCT-2020
1.1	Updated to: reflect new version of protocol (v8); edit purpose of SAP to reflect final analysis (rather than preliminary analysis); define secondary endpoints (section 1.5.2) and translational endpoints (section 1.5.3); include timing of final planned analysis (section 2.4.3); clarify handling of withdrawal and missing data (section 2.7); include derivation of RECIST measures, in new section (2.8.4); update references section to include new references in section 2.8.4; change patient disposition to reflect end of trial (section 3.1); update estimand description for OS and PFS (section 3.6.1 and 3.6.2); clarify secondary endpoint of best response (section 3.7); update Table 1 to remove "number of subjects ongoing" to reflect end of study analysis; clarify use of investigator-reported progression in Tables 13 and 14; add PD-L1 categories to Table 15; include plots of log cumulative hazard versus time and Schoenfeld residuals for primary analyses of OS and PFS (section 4.6); update table headings (to refer to database forms) and footnotes (throughout section 4).	Sean Ewings	11-APR-2022
1.2	Updated to include requested changes by Dean Fennell (waterfall plot, spider plot, landmark analyses, and additional variables in the forest plot)	Sean Ewings	26-MAY-2022
3.0	Updated to include changes requested by Dean Fennell, added in section 5.7.2 (table 12 and 13) to provide duration of response and time to response information.	Kayleigh Hill	11-AUG-2022