Statistical analysis

MUK*nine a*

Analyses using response and progression data will be performed using the data recorded on the CRF. The data recorded on the CRF may be centrally reviewed to assess the quality of these data.

Screening population

The screening population will include all participants who are registered into MUK *nine a*, regardless of their risk assessment. Participants for whom we do not receive a risk assessment result will be included in this population.

Non-MUK *nine b* population

The Non-MUK nine b population will include all participants who are registered into MUK *nine a*, regardless of their risk assessment, who are not registered into the MUK *nine b* trial. Participants for whom we do not receive a risk assessment result will be included in this population.

Non-MUK *nine* b high risk population

The high risk population will include all participants who are assessed as being high risk, but who are not registered into the MUK *nine b* trial.

Non high risk population

The non-high risk population will include all participants who are assessed as being not high risk. Participants for whom we do not receive a risk assessment result will not be included in this population.

Analyses will be performed for the four populations separately, unless specified.

Imaging study population

The imaging study population will contain all participants who have entered the imaging sub-study and had a diffusion-weighted whole body MRI scan at baseline.

Primary endpoint analysis

The number and proportion of molecular risk-defining investigations performed within 8 weeks will be reported. Summary statistics of the length of time taken to turn around molecular risk-defining investigations will also be reported, including median, mean, standard deviation, inter-quartile range (IQR). This will be summarised for the screening population.

Brown S, *et al*. *BMJ Open* 2021; 11:e046225. doi: 10.1136/bmjopen-2020-046225

Secondary endpoint analysis

Recruitment rates

The number of participants registered overall and the average rate per month will be reported. The number and proportion of participants identified as high risk (out of both the number of participants registered to MUK *nine* a and the number of participants registered and with a corresponding sample taken for risk definition) overall will also be reported, as well as the number and proportion of participants accepting registration to MUK *nine* b (out of the number identified as high risk). Summaries will be provided overall and by site.

Progression-free survival

Progression-free survival curves will be calculated using the Kaplan-Meier method and the median progression-free survival estimates and progression-free survival estimates at yearly time-points with corresponding 95% confidence intervals will be presented for the Non-MUK *nine b* population, the Non-MUK *nine* b High risk population and the Non high risk population..

The Cox proportional hazards model (if appropriate), adjusting for treatment received first-line, will also be used to summarise progression-free survival for each population. Covariate estimates, standard errors, hazard ratios, 95% confidence intervals, as well as p-values will be presented for all variables incorporated in the model.

The Cox proportional hazards model, adjusting for treatment received first-line and other pre-specified baseline characteristics, may be used to further summarise progression-free survival, after discussion with the MUK *nine* Trial Management Group (TMG). The number of characteristics (and their factors) included in the model will depend on the number of participants in the relevant population.

Second progression-free survival (PFS2)

PFS2 curves will be calculated using the Kaplan-Meier method and the median second progression-free survival estimates and progression-free survival estimates at appropriate time-points with corresponding 95% confidence intervals will be presented for the Non-MUK *nine b* population, the Non-MUK *nine* b High risk population and the Non high risk population..

The Cox proportional hazards model (if appropriate), adjusting for treatment received first and second-line, will also be used to summarise PFS2 within each population. Treatment received second-line will be included using a time-dependant covariate to incorporate timing of treatment. Covariate estimates, standard errors, hazard ratios and 95% confidence intervals, as well as p-values will be presented for all variables incorporated in the model.

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The Cox proportional hazards model, adjusting for treatment received first-line and other pre-specified baseline characteristics, may be used to further summarise second progression-free survival, after discussion with the MUK *nine* TMG. The number of characteristics (and their factors) included in the model will depend on the number of participants in the relevant population.

Treatment received first and second-line

Treatment received first and second-line will be summarised in a tabular form, along with reasons for stopping treatment. This will be summarised for the Non-MUK *nine* b population, the Non-MUK *nine* b High risk population and the Non high risk population.

Response to first and second-line treatment

The number and proportion of participants in each response category post first and second-line treatment will be presented with corresponding 95% confidence intervals for each population and type of treatment for the Non-MUK *nine b* population, the Non-MUK *nine* b High risk population and the Non high risk population.

Overall survival

Overall survival curves will be calculated using the Kaplan-Meier method and median overall survival estimates and overall survival estimates at yearly time-points with corresponding 95% confidence intervals will be presented for the Non-MUK *nine b* population, the Non-MUK *nine* b High risk population and the Non high risk population.

The Cox proportional hazards model (if appropriate), adjusting for treatment received first and second-line will also be used to summarise overall survival within each population. Treatment received second-line will be included using a time-dependant covariate to incorporate timing of treatment. Covariate estimates, standard errors, hazard ratios and 95% confidence intervals, as well as p-values will be presented for all variables incorporated in the model.

The Cox proportional hazards model, adjusting for treatment received first-line and other pre-specified baseline characteristics, may be used to further summarise overall survival, after discussion with the MUK *nine* TMG. The number of characteristics (and their factors) included in the model will depend on the number of participants in the relevant population.

MUK*nine b*

Analyses using response and progression data will be performed using both the data recorded on the eCRF, and data from analysis of central samples. Primacy will be given to the central sample assessment of response, and local data recorded on the eCRF will be used

where a central assessment is not available. Differences between the local eCRF data and the central assessment data will be summarised.

Analysis population

The analysis population, as well as the safety population, will include all participants who receive at least one dose of any trial treatment.

Imaging study population

The imaging study population will contain all participants who have entered the imaging sub-study and had a diffusion-weighted whole body MRI scan at baseline.

Interim analyses

Interim assessments will be performed after cohorts of 10 participants have been registered to treatment and followed up to 120 days post-ASCT, until all participants have been recruited and received induction treatment.

The trial may be terminated early for futility based on MRD status at 100 days post-ASCT and PFS at 100 days post-ASCT. If a participant does not receive an ASCT, the 100 days post-ASCT time-point becomes 12 months post registration as this is approximately equivalent.

At each interim analysis, the posterior probabilities of the two events in terms of pre-defined cut-points are calculated in order to determine whether the trial should be stopped for futility.

Primary endpoint analysis

At the end of the study, the experimental treatment arm will be compared to the historical control prior in terms of PFS at 18 months post-registration/randomisation for the MUK *nine* b analysis population. If the proportion of participants who are alive and progression-free at 18 months post-registration is higher in the treatment arm than in the control prior with 85% probability, the treatment arm will be deemed efficacious.

Further analyses of progression-free survival at 18 months post-registration will also be performed outside of the Bayesian framework. PFS curves will be calculated using the Kaplan-Meier method and median progression-free survival estimates and progression-free survival estimates at 6, 12 (corresponding approximately to the 100 days post-ASCT time-point) and 18 months with corresponding 95% confidence intervals will be presented.

At the end of the study, the experimental arm will be independently compared to historical control data using molecularly matched individual participant data (IPD) from Myeloma XI/XI+ and assessed for superiority in terms of progression-free survival (PFS) at 18 months post-registration/randomisation in an exploratory analysis.

Secondary endpoint analysis

Although not an endpoint, baseline characteristics will be summarised for participants in the analysis population. All MUK nine b secondary endpoint analyses will be performed for the MUK nine b analysis/safety population.

Safety

The number of SAEs will be summarised and presented by MedDRA system organ class. In addition, information will be given on the number of SAEs per participant, together with details on the causality, expectedness and outcome of each SAE experienced. Summaries of SARs and SUSARs will also be presented.

Toxicity

Summaries will be produced to show the proportion of participants experiencing each grade of toxicity overall, presented overall and by other groupings, such as stage of treatment, as necessary.

Progression-free survival at 100 days post-ASCT

Progression-free survival at 100 days post-ASCT is used to determine whether the trial should be stopped for futility, as detailed above. The 100 days post-ASCT time-point is approximately equivalent to 12 months post-registration, and progression-free survival estimates at this time-point are presented as part of the primary endpoint, detailed above.

Minimal residual disease (MRD) at the end of induction therapy, 100 days post-ASCT and post-consolidation part 2

MRD status will be assessed at the end of induction therapy, 100 days post-ASCT and 1 year post-ASCT for all participants, regardless of their categorical paraprotein response.

MRD status will be summarised at each time-point. These summaries will be obtained using multi-level repeated measures models accounting for data at all time-points, regardless of timing of sample for the time-point not of interest, assuming missing data at random [MAR], allowing for time and adjusting for pre-specified clinically important baseline characteristics [all fixed effects] and for participant and participant-time interaction [random effects] where appropriate.

Data will also be summarised descriptively using plots of proportion of participants with MRD negative disease over time and summary tables. Missing data patterns will be examined carefully and sensitivity analyses using different missing data assumptions will be performed if appropriate.

Sensitivity analyses may be carried out using methods such as multiple imputation or pattern-mixture multi-level models categorising participants into strata based on clinical information which is believed to represent the reasons for missing data (assuming MAR data conditional upon participants' clinical data).

Overall survival

Overall survival curves will be calculated using the Kaplan-Meier method and median overall survival estimates and overall survival estimates at 12, 24 and 36 months with corresponding 95% confidence intervals will be presented by treatment group.

The Cox proportional hazards model (if appropriate), adjusting for pre-specified baseline characteristics, may be used to further summarise overall survival, after discussion with the MUK *nine* TMG. The number of characteristics (and their factors) included in the model will depend on the number of participants in the analysis population.

Maximum response at the end of induction therapy, 100 days post-ASCT and post-consolidation part 2

The number and proportion of participants in each maximum response category will be presented with corresponding 95% confidence intervals at each time-point. Participants who do not achieve a maximum response will be summarised as 'no maximum response'.

Overall response at the end of induction therapy, 100 days post-ASCT and post-consolidation part 2

The proportion of participants achieving at least PR will be summarised with corresponding 95% confidence intervals, at each time-point.

Time to progression

Time to progression will be summarised using cumulative incidence function curves, and median time to progression estimates with corresponding 95% confidence intervals will be presented.

An assessment based on the number of participants who die with no previous evidence of disease progression (i.e. the number of competing risk events) will be made as to whether time to progression should be summarised using the Kaplan-Meier method (i.e. not incorporating competing risks).

Time to maximum response

Time to maximum response curves will be calculated using the Kaplan-Meier method, and the median time to maximum response estimates with corresponding 95% confidence intervals will be presented.

As maximum response is defined as SD or better, the number of participants who progress or die without achieving a maximum response is expected to be small. This will be monitored on an ongoing basis via DMEC reports and an assessment will be made as to whether analyses that take into account competing risks (for example cumulative incidence function curves) are required.

Second progression-free survival (PFS2)

PFS2 curves will be calculated using the Kaplan-Meier method and the median second progression-free survival estimates and progression-free survival estimates at appropriate time-points with corresponding 95% confidence intervals will be presented.

The Cox proportional hazards model, adjusting for pre-specified baseline characteristics, may be used to further summarise second progression-free survival, after discussion with the MUK *nine* TMG. The number of characteristics (and their factors) included in the model will depend on the number of participants in the analysis population.

Overall treatment benefit and clinician assessment of treatment benefit at the end of induction therapy and 100 days post-ASCT

The proportion of participants achieving each score for overall treatment benefit, and each response given to the clinician assessment of treatment benefit question, will be summarised with corresponding 95% confidence intervals, at each time-point.

A cross-tabulation of overall treatment benefit and clinician assessment of treatment benefit will be created to compare the two measures.

Quality of life

Quality of life will be summarised at each post-registration time-point, adjusting for baseline mean scores and 95% CIs. These summaries will be obtained using multi-level repeated measures models accounting for data at all post-baseline time points, regardless of time of completion for the time-point not of interest, assuming missing data at random [MAR], allowing for time and adjusting for baseline QoL and pre-specified clinically important baseline characteristics [all fixed effects] and for participant and participant-time interaction [random effects] where appropriate.

Brown S, *et al. BMJ Open* 2021; 11:e046225. doi: 10.1136/bmjopen-2020-046225

Data will also be summarised descriptively using bar charts, box plots, plots of mean QoL over time and summary tables. Missing data patterns will be examined carefully and sensitivity analyses using different missing data assumptions will be performed if appropriate.

Treatment compliance

Information on dose delays, reductions and omissions will be summarised by stage of treatment. Information on the proportion of participants with at least one dose delay, reduction or incidence of missed doses will also be presented overall and by stage of treatment.

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