STATISTICAL ANALYSIS PLAN

Treatment of myeloma cast nephropathy

The MYRE Study
Statistical Analysis Plan
(SAP)

Version: 1

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1 DATA SOURCE

The eCRF data were extracted then, structured by data managers. See Appendix reporting the Data Handling Manual of the study.

2 ANALYSIS OBJECTIVES

The objectives of the analysis are to provide estimates of treatment effect, using all defined end points, based on comparison of those end points according to the randomized treatment arm.
Point estimates with 95% confidence intervals are to be provided.

For ethical safety concerns, an interim analysis will be carried out one year after the start of randomization, or when 40 patients requiring no extra-renal treatment and 20 dialysis patients have been randomized.
It will concern tolerance and mortality, and its results will be communicated to the Independent Test Committee. To the extent that the intermediate analysis does not concern the comparison of the main endpoint, no adaptation of the type I error rate will be realized.

3 ANALYSIS SETS/ POPULATIONS/SUBGROUPS

The two parts (Haemodialysis and non Haemodialysis patients) of the study will be analyzed separately.
Analyses will be performed in a modified intention-to-treat basis, that is, only patients who violated the eligibility criteria or those with consent withdrawal, could be excluded from the analysis.

4 ENDPOINTS AND COVARIATES

Haemodialysis patients
The primary endpoint is the prevalence of dialysis independence at 3 months post-randomization.
Independence is defined on eGFR value ≥15 ml/min/1.73m² at least 15 days after the last session.

Non Haemodialysis patients
The primary endpoint is the improvement of renal function after 3 protocol chemotherapy cures (at the latest 3 months after randomization), which is defined on serum creatinine value ≤ 170 μmol / l or a GFR estimated according to the modified MDRD equation ≥ 40 ml / min /1.73m² (a criterion corresponding to a renal function level compatible with intensive myeloma treatment).
Secondary endpoints are:
- Prevalence of dialysis independence and eGFR value at 6 and 12 months
- Haematological response after 1 and 3 cycles of chemotherapy, at 6 and 12 months
- Event free survival (EFS)
- Overall survival (OS)
- Adverse events (AE)

Haematological response is defined on variation of the involved sFLC as the main parameter. Partial response (PR) and very good partial response (VGPR) were defined by $\geq 50\%$ and $\geq 90\%$ sFLC reduction, respectively. Complete response (CR) was defined by normal sFLC level and kappa/lambda ratio with negative serum and urine immunofixation and, for stringent CR, by $<5\%$ plasma cells in bone marrow. In hemodialyzed patients, progressive disease (PD) or relapse were defined by a $\geq 25\%$ increase from baseline of the culprit sFLC (or of serum entire monoclonal Ig level, if present) or by any non-renal myeloma defining event. Otherwise, International Myeloma Working Group criteria were used.

5 HANDLING OF MISSING VALUES AND OTHER DATA CONVENTIONS

Missing data will be imputed. Simple or multiple imputation techniques will be used according to the amount and underlying potential mechanisms of missingness.

6 STATISTICAL METHODOLOGY

6.1 STATISTICAL PROCEDURES

Binary outcomes measured will be estimated using punctual estimates with 95% confidence interval. Treatment effect will be measured by odds ratio estimated from logistic model.

Comparisons between the randomization groups on the secondary endpoints will be based on appropriate bilateral formulation tests. The continuous criteria will be compared by Mann and Whitney rank tests; Qualitative criteria by chi2 tests or exact Fisher tests; The censored criteria by log-rank tests, unless there is competition (or informative censoring) of the observations, in which case a cumulative incidence will be estimated and comparison based on Gray tests. Failure-time data (overall survival and event-free survival) will be computed from date of randomization, estimated by the Kaplan Meier method, then compared by the log-rank test, with treatment size effect measured by hazard ratios (HR) estimated from Cox models. Proportional hazards assumptions will be checked.
Safety will be evaluated by the incidence rates of reported severe adverse events by patient-years of treatment exposure.

6.2 MEASURES TO ADJUST FOR MULTIPLICITY, CONFOUNDERS, HETEROGENEITY, ETC.

To adjust for potential confounding, odds ratios adjusted on potential prognostic factors selected by univariable analyses at the 10% level, will be computed.

The center effect will be studied.

The threshold of significance will be set at 5% for all the tests of the statistical terminal analysis, which will therefore intervene at the end of the inclusions.

7 SENSITIVITY ANALYSES

No sensitivity analysis is planned.

8 PROGRAMMING PLANS

All analyses will be based on SAS (SAS Inc, cary, NC) and R (http://www.R-project.org) packages.
If applicable, provide the following in the appendix:

- Definition and use of visit windows in reporting
- Definition of Analysis Populations/Sets
- Further Definition of Endpoints
- Statistical Methodology Details