

Statistical Analysis Plan

The primary objective of this study is to assess safety and toxicity. The primary endpoint is the Maximum Tolerated Dose (MTD) of the combination of fractionated docetaxel and Ra-223. This is defined as the maximum Dose Level explored in which the DLT rate is less than 33% at the beginning of cycle 2.

The secondary objectives of this trial are:

- Progression-Free Survival
- Time to Treatment Failure
- Objective Response Rate
- Overall survival
- Ability to complete six cycles of combination therapy
- PSA Kinetics
- Quality of Life
- Bone Marker Outcomes

These are defined in the protocol.

The definitions of the study populations are listed below.

Population	Definition
Enrolled	This will comprise all subjects who meet the eligibility criteria and are registered onto the study.
Evaluable	This will comprise all subjects who complete the docetaxel lead-in and receive at least one dose of combination docetaxel AND Ra-223.

Subjects intolerant of docetaxel in the lead-in period will be removed from the trial and replaced from the study.

Maximum Tolerated Dose

In the dose escalation cohort, the MTD will be determined at the time the last subject in the study is due to begin cycle 2 of combination treatment. It will be determined by the highest dose level explored associated with less than a 33% DLT rate in the first cycle of combination therapy.

Progression Free Survival

Subjects from the dose escalation and expansion cohorts whose disease has not progressed by EOT visit will be followed every 12 weeks. PFS will then be calculated as a time-to-event endpoint and estimated with the Kaplan Meier method and swimmer plot. The historical median progression-free survival following docetaxel based therapy for metastatic castration-resistant prostate cancer is approximately 6 months.^{13,14} With a sample size of 37-43 evaluable subjects, the dose escalation and expansion cohorts will have a 73-79% power to detect a 50% increase in median PFS from 6 to 9 months, at the significance level of 0.05, with a one-sided test. The time to completion of accrual

(dose escalation and expansion cohorts) is projected at 24 months with a follow-up time of 12 months following last participant entry.

Time to Treatment Failure (TTTF)

Once Treatment Failure is met, TTTF will be calculated as a continuous variable, described with a swimmer plot and estimated with the Kaplan Meier method.

Overall Survival

Once disease progression is documented, subjects will enter a survival follow up period every 3 months until death. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate. Overall survival will be annotated as a continuous variable after death occurs and estimated using the Kaplan Meier method.

Objective Responses

These will be annotated as a continuous variable and described as proportions.

Ability to complete 6 cycles of combination therapy

After the last treatment on study, the number of subjects who were able to receive all doses of docetaxel and Ra-223 on time will be annotated as a proportion.

Continuously Measured Secondary Outcomes (PSA, Quality of Life, Bone Marker Outcomes)

For the continuously measured secondary outcomes (PSA, Quality of Life and Bone Marker Outcomes), we will calculate the descriptive statistics (means and standard deviations) at each time point (number of days) when the outcome data are collected. These will use continuous variables (PSA value, BPI and FACT-G questionnaire results for Quality of Life and bone-specific alkaline phosphatase and urine N-telopeptides for bone markers). Since these outcomes are repeatedly measured over time on a subject, we will also use mixed effect models to explore the temporal trajectories for the outcome changes over time in response to the treatment. The mixed effect models will be used for non-hypothesis driven purpose, i.e. no statistical comparisons will be made from these models. Rather, these models will allow us to explore the outcome change over time by accounting for the random intercepts and slopes among projected trajectory lines for all individuals. The overall projected trajectory lines can then be plotted for visual inspections and can serve as the foundation of generating the hypothesis for the future studies.

PSA kinetics will additionally be annotated as waterfall plots. We will also calculate PSA Response Rate of > 50% and > 90% as a categorical variable and these will be described as proportions. And bone-specific alkaline phosphatase and urine N-telopeptides changes will be also annotated with waterfall plots.

References

13. Petrylak, D., Tangen, C., Hussain, M., et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med.* 2004;351.15:1513-1520.

14. Morris, M., Lortol, Y., Sweeney, C., et al. Updated results: A phase I/IIa randomized trial of radium-223+ docetaxel versus docetaxel in patients with castration-resistant prostate cancer and bone metastases. *J Clin Oncol.* 2016; 34:Suppl 15: 5075-5075.