Randomized Phase II Trial of Radium-223 (RA) plus Enzalutamide (EZ) vs. EZ alone in Metastatic Castration Refractory Prostate Cancer (mCRPC): Final Efficacy and Safety Results.

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Background: We previously reported that treatment with EZ+RA was associated with a decline in serum bone metabolism markers (BMM), which correlated with improved outcomes compared to EZ alone (Agarwal N et al, Clinical Cancer Research, 2020, PMID 31937614). Here we report the final efficacy and safety results for this trial.

Methods: In this phase 2 trial (NCT02199197), patients (pts) with progressive mCRPC were treated with EZ (160 mg daily) ±RA (standard dose of 55 kBq/kg IV Q4 weeks x 6), until disease progression or unacceptable toxicities. Primary objectives of change in bone markers and safety have been reported previously. Secondary objectives included comparison of PSA progression free survival (PFS),overall survival (OS), and long term safety in all pts receiving RA+EZ vs EZ alone. Post hoc analysis included comparison of PSA-PFS2 (defined as time from start of protocol therapy to PSA progression on subsequent therapy or death whichever occurred earlier), time to subsequent/next therapy (TTNT), and long term safety. Survival analysis and log-rank tests was performed using the R statistical packagev.4.0.2 (https://www.r-project.org). Statistical significance was defined as $P < 0.05$.

Results: Between 08/2014 and 11/2017, 47 pts were eligible and enrolled. Median follow up was 22 months (range 3.2-71.5). Thirty-five pts received RA+EZ and 12pts received EZ alone. Receipt of prior abiraterone was allowed and was balanced between two groups: 60% in RA+EZ vs. 64% in EZ pts. Final efficacy results: TTNT, PSA-PFS2 were significantly improved in the RA+EZ pts over EZ alone pts, and all other efficacy parameters were numerically improved in RA+EZ pts (TABLE). Final safety results: none of the 12 EZ alone pts had any fracture; two of 35 RA+EZ pts were found to have incidental grade 1 asymptomatic fracture at the site of bone metastasis on routine imaging, at 15 and 31 months respectively after the last dose of RA, and did not require any intervention. No patients developed bone marrow disorders during the follow-up period. Efficacy and safety data will be elaborated during the meeting.

Conclusions: In our study, EZ+RA resulted in significant long-term clinical benefit over EZ alone in pts with mCRPC without compromising safety. * NA&BLM; equal contribution

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Endpoint	**EZ+RA (n = 35)**	**EZ (n = 12)**	**P-value**
PSA-PFS, Median Months (95% CI)	8.9 (4.73-21.4)	3.38 (2.7-NA)	0.97
PSA-PFS2, Median Months (95% CI)	18.7 (12.2-42.8)	8.41 (5.52-NA)	0.033
TTNT, Median Months (95% CI)	15.9 (9.7-35.5)	3.47 (3.3-NA)	0.067
OS, Median Months (95% CI)	30.8 (17.9-NA)	20.6 (16.8-NA)	0.73