Randomized Phase II study evaluating the addition of pembrolizumab to radium-223 in metastatic castration-resistant prostate cancer.

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Background: Treatment (tx) options for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) to bone are limited. Radium-223 (R223) has demonstrated overall survival (OS) benefit, but objective clinical responses to R223 and the anti-PD1 checkpoint inhibitor (CPI) pembrolizumab (pem) are infrequent. As R223 may increase immunogenicity of mCRPC to bone and increase activity of CPI, we undertook a Phase 2 study to assess the safety of the combination and differences in immune cell infiltrate in bone biopsies (bx) and preliminary clinical activity of R223 + pem vs. R223 alone.

Methods: Eligibility required mCRPC to bone with no visceral metastases (mets) or lymph nodes > 2 cm, ECOG PS 0 or 1, Hgb ≥ 9 g/dl, and no prior R223 or CPI. Pts underwent bone bx at screening and at 8 wks; if tumor was not seen on initial screening bone bx, pts were required to undergo 2nd attempt. Pts were stratified by alkaline phosphatase ≥220 vs. < 220 U/L and high vs. low volume bony mets (CHAARTED criteria) and randomized 2:1 to receive R223 55 kBq/kg q4wks + pem 200 mg q3wks (Arm A) or R223 55 kBq/kg q4wks alone (Arm B). Restaging was performed q12wks. If initial restaging after 3 doses R223 showed at least stable disease, pts in Arm A continued pem alone until progressive disease (PD). Upon PD, R223 was resumed if no new visceral mets. Pts continued tx until clinical/radiologic PD, unacceptable toxicity or completion of 6 doses of R223. The primary endpoint was difference in CD4+ and CD8+ T cell infiltrate in 8 week vs. baseline bx; secondary endpoints were safety/tolerability, radiographic progression-free survival (rPFS) and OS. Exploratory endpoints included PSA response and rate of symptomatic skeletal events (SSEs).

Results: Of the 45 pts enrolled, 42 received study tx (29 Arm A, 13 Arm B) and were eligible for analysis. 21 pts in Arm A and 5 in Arm B had evaluable paired bone bx. Median fold-change of proportion of CD4+ T-cells/total from baseline to 8 wks was 0.90 (range 0.0-26.6) in Arm A and 0.40 (range 0.0– 13.0) in Arm B (P=0.87); for CD8+ cells, median 0.67 (range 0.0 – 40.4) in Arm A and 0.40 (range 0.1 – 28.8) in Arm B (P=0.77). Grade 3 treatment-related non-hematologic adverse events occurred in 3 pts (10%) in Arm A (pneumonitis, diarrhea, AST increased) with none in Arm B. Median rPFS was 6.7 mo (95% CI 2.7 - 11.0 mo) in Arm A and 5.7 mo (2.6-NR) in Arm B; median OS was 16.9 mo (12.7-NR) in Arm A and 16.0 (9.0-NR) in Arm B. 3 pts (10%) in Arm A and 0 in Arm B had PSA reduction of ≥ 50%. SSEs occurred in 11 pts (38%) in Arm A (0 pathologic fractures) and 7 (54%) in Arm B (3 pathologic fractures).

Conclusions: While bone biopsies were hampered by nondiagnostic sampling, there was no evidence for increased CD4+/CD8+ T cell infiltration with the combination of R223 with pem, and no evidence for prolongation of rPFS or OS compared to R223 alone. Additional biomarker analyses will be presented. R223 + pem can be safely combined with no unexpected toxicities and could serve as a backbone for the addition of other therapeutic strategies.

Clinical trial information: NCT03093428.