We hypothesized that Ra223 in combination with enza would induce a higher degree of immune activation and clinical response than enzalutamide alone in patients with mCRPC.

Methods Patients were randomized 2:1 to Arm A (enza + Ra223) or Arm B (enza only). Blood was collected at start of treatment and evaluated by flow cytometry to measure immune activation or exhaustion after ≥3 months on study, and by Luminex for cytokines after 1 month on study. A Kaplan-Meier model was used to calculate survival data. Expression of immune correlatives were log-transformed and analyzed with the Wilcoxon Rank Sum test to detect differences between the two arms.

Results A total of 28 patients were enrolled, whose median age was 68 (57–87). 6 are Hispanic (21%) and 2 each are African American or Asian (7%). Median duration of follow up was 8.3 (1.8–29.9) months (mo). 9 pts (36%) had visceral metastases. Arm A showed significantly greater increase in PD-L2 expression after treatment compared to Arm B (p = 0.0026). There was otherwise no significant difference between the two arms for flow cytometry markers. Cytokines remained low generally, except for IL10 and TNFa, elevated in 5 and 2 patients, respectively. 9 of 21 (48%) in Arm A had SD or PR as best RECIST response compared to 3 of 9 (33%) in Arm B. PSA response was not different between the arms. Arm A had PFS of 8.8 (3.6–29.9+) mo while PFS was 5.3 (3.4–12.2+) mo in Arm B. 4 (27%) patients in Arm A and 3 (50%) patients in Arm B stopped treatment due to disease progression. No grade 3 adverse events were observed in either arm and no unexpected toxicities occurred.

Conclusions Although Ra223 with enza did not show increased PD-L1 expression as seen in pre-clinical mouse models treated with Ra223, the combination did significantly induce PD-L2 expression in this study and raise the potential of improved treatment efficacy with the addition of an immune checkpoint inhibitor as suggested in these pre-clinical models.1 Despite the lack of augmentation of humoral response, combination treatment paradoxically showed better clinical response, consistent with prior studies involving Ra223 and Sipleucel-T immunotherapy.2

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REFERENCES

Ethics Approval This study was approved by the IRB of the University of Southern California and the IRB of City of Hope.