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Biomarker analysis of men with enzalutamide (enza)-resistant metastatic castration-resistant prostate cancer (mCRPC) treated with pembrolizumab (pembro) + enza in KEYNOTE-199

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Background

In KEYNOTE-199 (NCT02787005), pembro + enza had durable antitumor activity in enza-refractory mCRPC. We evaluated the association between prespecified biomarkers and clinical outcomes.

Methods

Cohorts 4 (C4; RECIST-measurable disease) and 5 (C5; nonmeasurable, bone-predominant disease) enrolled men with chemotherapy-naive mCRPC, irrespective of PD-L1 status, that progressed after initial response to enza. We evaluated TMB by whole exome sequencing (n = 64), PD-L1 combined positive score (CPS) by IHC (n = 124), and 18-gene T-cell–inflamed gene expression profile ($Tcell_{inf}$GEP) by NanoString (n = 51). Outcomes were DCR, PFS, PSA response, PSA progression, OS, and ORR per blinded independent review (C4 only). Significance of continuous biomarkers (CPS, TMB, GEP) was prespecified at 0.05 for 1-sided *P* values from logistic (ORR, DCR, PSA response) and Cox proportional hazard (PFS, OS, PSA progression) regression adjusted for ECOG PS.

Results

In C4, ORR was 10% (5/48) in pts with evaluable TMB data and 12% (10/81) in pts with CPS data. In C4 and C5, 16% (10/64) and 14% (17/124) of pts with TMB and CPS data, respectively, achieved a PSA response. TMB was significantly associated with DCR ($P = 0.03$) and trended toward an association with PSA response ($P = 0.08$). TMB (AUROC [95% CI]: 0.68 [0.51-0.86]), but not CPS (0.54 [0.41-0.67]) or $Tcell_{inf}$GEP (0.55 [0.37-0.74]), enriched for PSA response. TMB ($P = 0.04$), but not CPS ($P = 0.57$) or $Tcell_{inf}$GEP ($P = 0.32$), was significantly associated with PSA progression. There was 1 MSI-H pt (per Promega PCR assay); this pt achieved an objective and PSA response and had PFS >6 months. TMB, CPS, and $Tcell_{inf}$GEP were not associated with PFS or OS. There was a low prevalence of TMB ≥175 mut/exome (11%) and $Tcell_{inf}$GEP-high (≥–0.318; 16%).

Conclusions

In this biomarker analysis of KEYNOTE-199 C4-C5, PD-L1 CPS and $Tcell_{inf}$GEP were not significantly associated with clinical outcome. Despite the low prevalence of TMB ≥175 mut/exome, TMB was positively associated with outcomes of pembro + enza in pts with mCRPC. The sample sizes for the exploratory analyses were small, and results should be interpreted with caution.

Clinical trial identification

NCT02787005.

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Disclosure

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