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Abstract:

Combination of a poly ADP-ribose polymerase (PARP) inhibitor with a T cell receptor β chain–directed antibody fusion molecule in immune-excluded prostate tumor models

Background

Metastatic castration-resistant prostate cancer (mCRPC) is an aggressive disease with limited response to systemic therapy despite testosterone suppression. STAR0602 is a selective, bifunctional T cell agonist composed of an antibody targeting Vβ6 and Vβ10 T cell receptors (TCRs) fused to human interleukin-2, that selectively expands specific Vβ6+ CD8+ memory T cells and has shown clinical activity as a monotherapy in anti-PDL-1 resistant tumors (NCT05592626). Here, we studied the combination of mSTAR1302, the murine surrogate of STAR0602, with the PARP inhibitor olaparib in immune-excluded prostate cancer models.

Methods

TRAMP-C2 and RM-1, immunologically “cold” murine prostate cancer models, were used to assess antitumor activity and survival benefit after combination therapy treatment. Depletion studies were performed to determine the requirement of a subset of immune cells (natural killer (NK) cells, CD4+, CD8+, and Vβ13+ T cells) or interferon (IFN)- γ for the therapeutic efficacy of combination therapy with olaparib and mSTAR1302. Flow cytometry and RNA expression analyses were performed on tumors and spleens to assess the immune response.

Results

Combination therapy with olaparib and mSTAR1302 elicited significant tumor regression of TRAMP-C2 and RM-1 tumors and improved survival compared to either mSTAR1302 or olaparib alone. Combination therapy with olaparib and mSTAR1302 significantly increased the frequency of tumor-infiltrating lymphocytes (TILs), expanded activated Vβ13+ CD4+

and Vβ13+ CD8+ T cells, decreased immunosuppressive cells, and increased the CD8+ T cell population with stem cell-like properties. Depletion studies demonstrated that Vβ13+ CD4+, Vβ13+CD8+, and NK cells, as well as IFN- γ are required for the antitumor efficacy of combination therapy with olaparib and mSTAR1302. A TRAIL-R2 knockout TRAMP-C2 model demonstrated the critical role of TRAIL-R2 in antitumor efficacy.

Conclusions

In summary, these data support the rationale for a planned clinical trial with olaparib and STAR0602 for mCRPC patients who have progressed on androgen deprivation therapy.