Targeting Advanced Prostate Cancer with Antibody-Drug Conjugate (ADC) Combinations

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Background: Antibody-Drug Conjugates (ADCs) are monoclonal antibodies targeted against an antigen on the cancer cell surface conjugated to a cytotoxic drug (payload) via a chemical linker. To date no ADCs are approved for metastatic castration-resistant prostate cancer (mCRPC) therapy due to a lack of efficacy and/or systemic toxicity. The rational design of ADCs and the development of combinatorial ADC-based approaches may enhance the therapeutic window for effective mCRPC treatment.

Methods: Distribution of mCRPC surface targets (B7-H3, PSMA, and STEAP1) was evaluated in mCRPCs using multiplex immunofluorescent staining to identify antigen pairs suitable for ADC co-targeting. Monoclonal antibodies binding target antigens were expressed in 293-F cells, purified, and characterized for ADC production. To select the payload pairs with synergistic interaction, a combinatorial payload screen was completed, and drug synergy was validated in a panel of mCRPC cell lines. Molecular mechanisms of drug interaction were studied in loss-of-function experiments *in vitro*. Synergistic ADCs were produced and tested in cellular and xenograft mCRPC models.

Results:

(1) The majority of mCRPC patients present with B7-H3 & STEAP1 double-positive metastasis.
(2) Genotoxic payloads (duocarmycin, doxorubicin, camptothecin analogs, pyrrolobenzodiazepines, calicheamcycin), as well as ADCs bearing genotoxic payloads, synergize with the Bcl-xl inhibitor A-1331852.
(3) P53 activity is predictive of mCRPC response to the combination of DNA damaging ADCs with systemic A-1331852.

Conclusions: This work addresses challenges associated with ADC monotherapy in mCRPC and explores the potential of rational ADC combinations. We nominate B7-H3 and STEAP1 as targets for dual ADC therapy, and we propose to use DNA-damaging agents and Bcl-xl inhibitor A-1331852 as payloads for B7-H3 and STEAP1-targeting ADCs. Synergistic interactions between genotoxic ADCs and ADCs bearing A-1331852 have the potential to elicit effective tumor killing in mCRPC. Because the prototypes of such ADCs have already demonstrated safety in early phase human studies, the data generated in this work enables near-term clinical development of new agents for mCRPC therapy.

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