ABSTRACT

Immunotherapy has transformed cancer treatment by unleashing potent and durable anti-tumor immunity against many cancers. However, these therapies can also induce systemic autoimmunity by activating autoreactive T cells in normal tissues. Combinations of checkpoint inhibitors targeting PD-1 and CTLA-4 increase clinical response rates but similarly increase toxicities, thereby reducing their clinical potential. New approaches are therefore needed that provide anti-tumor activity without dysregulating systemic immunity.

CytoMx has developed Probody therapeutics (Pb-Tx), which are proteolytically-activated antibodies (Abs) designed to widen the therapeutic index by minimizing drug interaction with normal tissue while retaining anti-tumor activity. Pb-Tx are “masked” to attenuate binding to target in healthy tissue but can become “unmasked” in the tumor microenvironment by tumor-specific protease activity.

In vitro, the masked PD-1 Pb-Tx had reduced affinity for mouse PD-1 relative to the parental antibody (Ab). In mice, single-agent Abs to CTLA-4 and to PD-1 as well as the PD-1 Pb-Tx induced 10%, 30%, and 20% complete tumor regressions (CRs) against established MC38 tumors, respectively. In combination with CTLA-4 Ab, both PD-1 Ab and PD-1 Pb-Tx induced 80% CRs and generated effective T cell memory against tumor re-challenge. In 10-week-old NOD mice, a 1 or 10 mpk single dose of anti-PD-1 antibody induced diabetes in 43% and 57% of mice, respectively, while a 10 mpk dose of PD-1 Pb-Tx yielded only 14% disease incidence with delayed onset. In younger NOD mice, the CTLA-4/PD-1 antibody combination induced diabetes in 50% of mice. In contrast, mice administered the PD-1 Pb-Tx/CTLA-4 antibody combination were completely protected.

INTRODUCTION

Probody Therapeutics are Protease-Activatable Antibody Prodrugs

Parental Antibody

Substrate Linker

- Stable in vivo in circulation
- Preferentially cleaved by tumor proteases

Protease

- Dysregulated activity of specific proteases in cancer cells

Masking Peptide

- Reduces antigen binding
- Released from Pb-Tx upon cleavage of substrate linker, producing a fully active antibody

RESULTS

Figure 1: PD-1 Pb-Tx is functionally masked and binds mouse PD-1 with decreased affinity relative to parental PD-1 Ab.

The anti-mouse PD-1 antibody engineered to contain a protease substrate and mask (PD-1 Pb-Tx) binds to immobilized mouse PD-1 with decreased affinity relative to parental Ab by standard plate ELISA in the absence of protease.

CONCLUSIONS

- A Probody therapeutic targeting the T cell inhibitory checkpoint receptor PD-1 (PD-1 Pb-Tx) demonstrates potent antitumor activity as a single agent and in combination with anti-CTLA-4 in the MC38 mouse tumor model.
- Combination treatment generated systemic and durable anti-tumor immunity that was fully effective against tumor rechallenge.
- As a single agent, PD-1 Pb-Tx provides 10-fold dose protection from induction of autoimmune diabetes in NOD mice relative to the parental Ab and protects against diabetes in younger mice when combined with anti-CTLA-4.
- Systemic delivery of PD-1 Pb-Tx provides effective localized anti-tumor activity with improved peripheral safety when combined with CTLA-4 blockade in preclinical studies, demonstrating the promise of Probody technology for enabling effective yet safer combination immunotherapies for cancer treatment.

REFERENCES

1. Wong et al. CRI-CIIT-EMT-1A4CR 2015

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