Targeting B7-H3 in Prostate Cancer: Preclinical Proof-of-Concept with MGC018, an Investigational Anti-B7-H3 Antibody-drug Conjugate

Juniper A. Scribner, Francine Z. Chen, Anushka De Costa, Ying Li, Michael Chiechi, Thomas Son, Jeff Hooley, Jonathan Li, Scott Koenig, Chet Bohac, Ezio Bonvini, Paul A. Moore, Deryk Loo

MacroGenics, Inc., Brisbane, CA and Rockville, MD

Abstract

Introduction

MGC018: A Clinical-stage Anti-B7-H3 ADC Therapeutic

B7-H3

- Member of the B7-family of immune regulators
- Overexpressed in primary and metastatic prostate cancer
- Overexpression in mCRPC correlates with disease severity and poor patient outcome

MGC018

- Comprised of a humanized antibody targeting B7-H3 (MAGA17)
- Conjugated to a duocarmycin-based DNA alkylating payload via native cysteines
- Selective peptide linker facilitates payload delivery
- Retains potency in multi-drug resistant lines
- Phase 1/2 clinical trial in advanced solid cancers in progress (NCT03729596)

Duocarmycin-based Linker Payload

si-eno-Duocarmycin hydroxycyanostilbene (DXycin) structure Anti-B7-H3

Results

Range of Expression of B7-H3 in Prostate Cancer

- MGC018 Mediates Cytotoxicity Toward Prostate Cancer Cell Lines
- MGC018 Induces Apoptosis and Markers of Immunogenic Cell Death
- Caspase 3/7 Activation of LNCaP Prostate Cancer Cells

Prostate Cancer

- Prostate cancer is the second most common cancer among men worldwide
- Most prostate cancers are adenocarcinomas
- In 2021, it was estimated that 248,530 men in the United States will be diagnosed with prostate cancer, and 34,110 will die from the disease
- Although prostate cancer is initially treatable, especially if detected early, about 20-30% of men will relapse after the five-year mark following initial therapy
- Thus, novel therapies to improve the prognosis of prostate cancer are needed

Objectives

- Define the expression profile and prevalence of B7-H3 in prostate cancer
- Evaluate the therapeutic potential of MGC018 in preclinical models of prostate cancer
- Explore the potential to enhance the antitumor activity of MGC018 in combination with PARPi or ARi

B7-H3 is Highly Expressed in Prostate Cancer

- B7-H3 is frequently overexpressed in prostate cancer
- 80% of primary prostate cancer samples showed B7-H3 membrane staining on the tumor epithelium with an H-score greater than 150
- MGC018 demonstrated potent cytotoxicity in vitro toward prostate cancer cells and enhanced activity in some lines when combined with inhibitors of PARPi or ARi
- MGC018 mediated apoptosis and induced markers of immunological cell death
- Caspase 3/7 activation, PARP cleavage, calpain translocation, and ATP inhibition
- MGC018 demonstrated potent antitumor activity in vivo toward CDX and PDX models of prostate cancer
- Enhanced antitumor activity in vivo was observed when MGC018 was combined with inhibitors of PARPi or ARi

These results support B7-H3-directed ADC-based treatment of prostate cancer with MGC018

A MGC018 phase 1/2 clinical trial in advanced solid cancers is in progress (NCT03729596)

Conclusions

Reference

American Cancer Society Publications: Cancer Facts & Figures, 13th Edition and the National Cancer Institute

Acknowledgments

DUA linker payload conjugated by terminal from Bioconjugate Designs, Shanghai, the Americas

©2022 MacroGenics, Inc. All rights reserved.