

Targeting B7-H3 in Prostate Cancer:

Legend: [Membrane H-Score, Cytoplasmic H-Score, Vascular Intensity].

Alamar Blue cytotoxicity assay. Antibody Binding Capacity determined by DAKO QIFIKIT.

Caspase 3/7 Activation of LNCaP Prostate Cancer Cells

Kinetic analysis of activated Caspase 3/7 using the Incucyte Live-Cell Analysis System.

Patterns in LNCaP Prostate Cancer Cells

24 Hours

─ MGC018 0.15 μg/mL

MGC018 Induces Apoptosis and Markers of Immunogenic Cell Death

Caspase 3/7 Activation and Induction of Damage-Associated Molecular

Cytotoxicity and Caspase 3/7 activity assayed using Promega ApoTox-Glo triplex assay. Supernatants assayed with Promega ENLITEN ATP assay and Lumit HMGB1 immunoassay. Lysate assayed for cleaved PARP with Invitrogen cPARP ELISA.

MGC018 Induced Calreticulin Translocation to the Surface of LNCaP Prostate

ATP Secretion

Untreated

(0.15 μg/mL)

→ MGC018 1 μg/mL → MGC018 0.1 μg/mL → MGC018 0.01 μg/mL → MGA017 10 μg/mL

72 Hours

Antibody Binding Capacity

Control ADC

Cancer Cells

MGC018

10 μg/mL

Preclinical Proof-of-Concept with MGC018, an Investigational Anti-B7-H3 Antibody-drug Conjugate

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Abstract

Introduction: Prostate cancer is the second most common cancer among men worldwide. In 2021, it is estimated that 248,530 men in the United States will be diagnosed with prostate cancer, and 34,130 will die from the disease. Although current treatments have success initially, development of resistance commonly leads to recurrence of an incurable castrate-resistant form of the disease. Thus, significant need for novel therapies to improve the outcome of castrate-resistant prostate cancer remains. B7-H3 (CD276), a member of the B7 family of immunomodulatory molecules, is overexpressed in primary and metastatic prostate cancer, and correlates with disease severity and poor clinical outcome. MGC018, a duocarmycin-based B7-H3 antibody-drug conjugate, is currently being evaluated in clinical studies. Here, MGC018 was explored preclinically to assess the potential for targeting B7-H3 in prostate cancer.

Methods: Immunohistochemistry studies were performed to define the expression of B7-H3 in prostate cancer tissue microarrays (TMA). In vivo efficacy studies were conducted with human prostate cancer cell line-derived xenograft (CDX) models to explore the antitumor activity of MGC018 as a single agent and in combination with Poly (ADP-ribose) polymerase (PARP) and androgen receptor (AR) inhibitors. Based on the results in the CDX studies, in vivo efficacy studies were extended to a panel of metastatic prostate cancer patient-derived xenograft (PDX) models, which exhibit heterogenous expression of B7-H3 and more closely mimic the biological characteristics of patient tumors.

Results: Staining of prostate tumor TMAs revealed high expression of B7-H3 in primary and metastatic prostate cancer. Of the prostate samples evaluated, 95% (38/40) of the tumor samples were positive for B7-H3 (H-score ≥ 20): 65% had H-scores greater than 200, while 20% and 10% had H-scòres between 101-200 and 1-100, respectively. MGC018 demonstrated in vitro cytotoxicity toward B7-H3-positive human prostate cancer cell lines. The in vitro cytotoxicity translated to potent antitumor activity in vivo toward prostate cancer CDX models, and the antitumor activity of MGC018 was enhanced when combined with inhibitors of PARP or AR. In PDX models of metastatic prostate cancer, MGC018 was active as a single agent toward heterogeneous B7-H3-expressing tumors, and combining MGC018 with inhibitors of PARP or AR led to a greater response in some models.

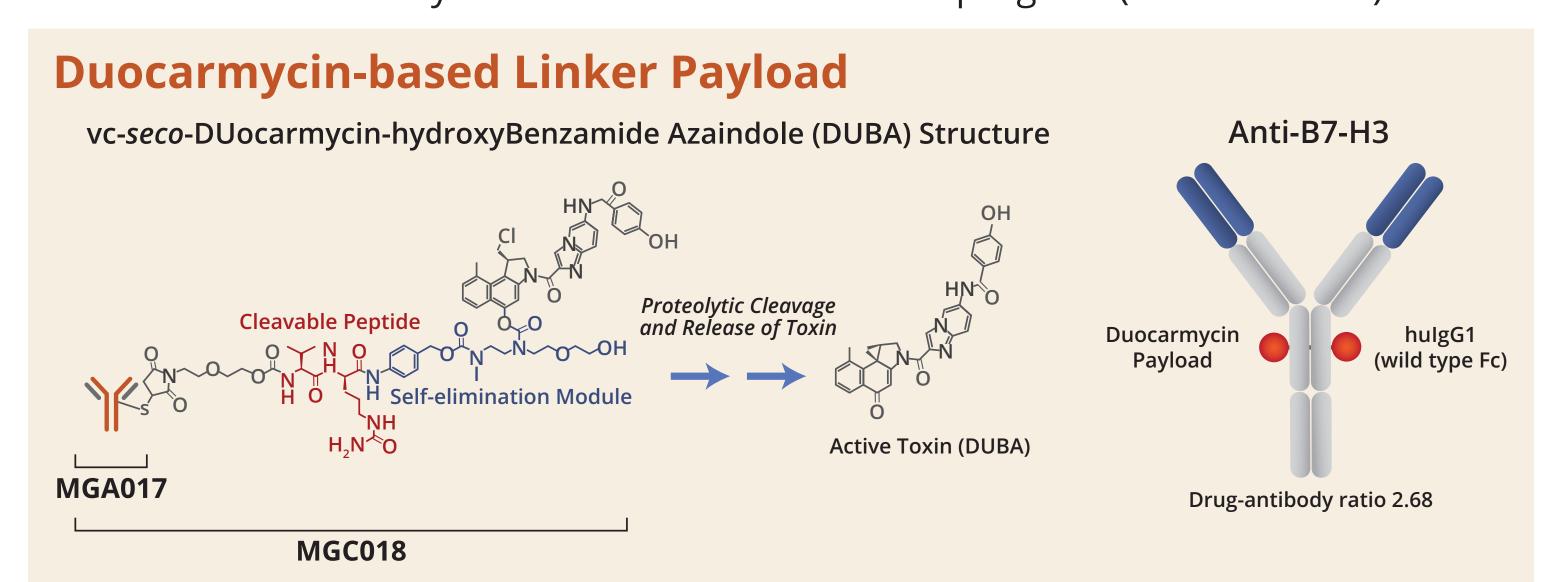
Conclusion: B7-H3 is frequently overexpressed in prostate cancer. MGC018 demonstrated potent antitumor activity in vivo toward CDX and PDX models of prostate cancer, and enhanced antitumor activity when combined with inhibitors of PARP or AR. These results support prostate cancer as an indication that may be responsive to ADC-based treatments directed toward B7-H3. MGC018 is being investigated in metastatic prostate cancer in a Phase 1/2 clinical study.

Introduction

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

B7-H3

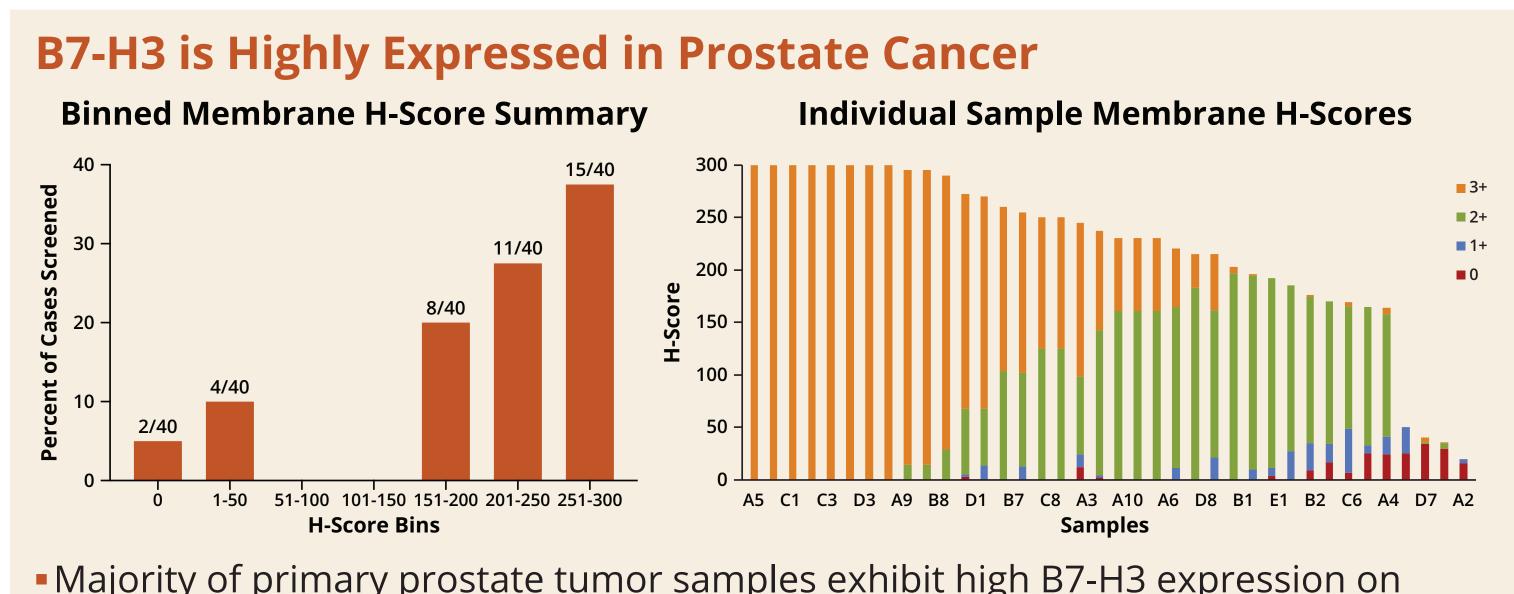
- Member of the B7-family of immune regulators
- Overexpressed in primary and metastatic prostate cancer
- Overexpression in mCRPC correlates with disease severity and poor patient outcome **MGC018**
- Comprised of a humanized antibody targeting B7-H3 (MGA017)
- Conjugated to a duocarmycin-based DNA alkylating payload via native cysteines
- Cleavable peptide linker facilitates bystander activity
- Retains potency in multi-drug resistant lines
- Phase 1/2 clinical study in advanced solid cancers in progress (NCT03729596)



Prostate Cancer

- Prostate cancer is the second most common cancer among men worldwide¹
- 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 34,130 will die from the disease¹
- Although prostate cancer is highly treatable, especially if detected early, about
- 20–30% of men will relapse after the five-year mark following initial therapy¹
- Thus, novel therapies to improve the outcome 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

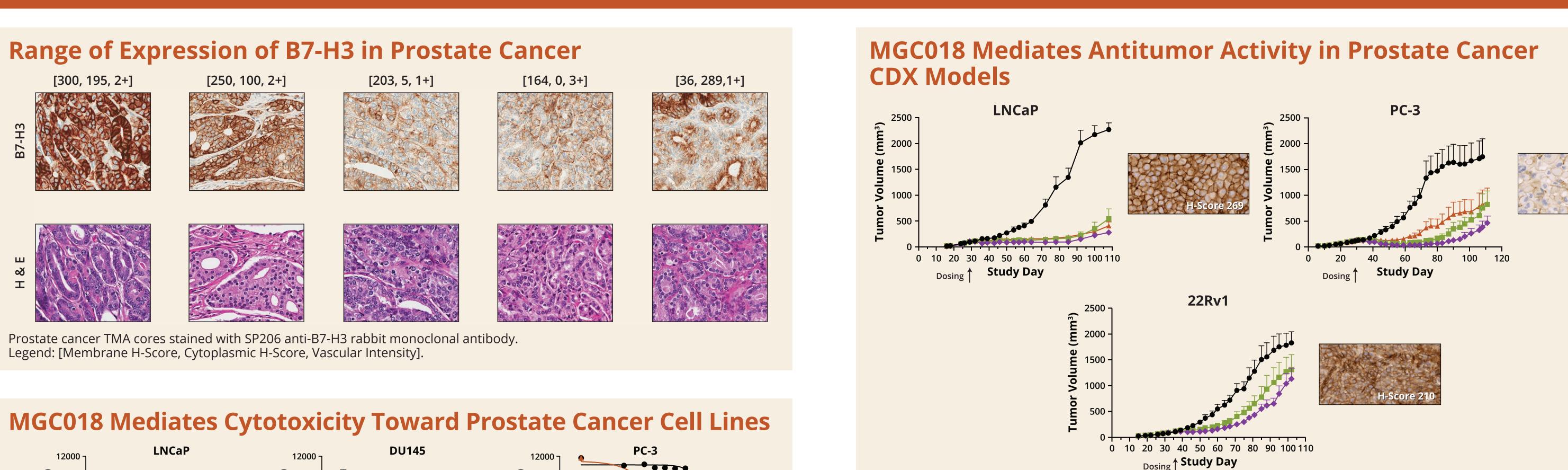
Results



 Majority of primary prostate tumor samples exhibit high B7-H3 expression on tumor epithelium

40 TMA cores stained with SP206 anti-B7-H3 rabbit monoclonal antibody.

Results



Vehicle → MGC018 10 mg/kg → MGC018 6 mg/kg → MGC018 3 mg/kg MGC018 shows dose-dependent antitumor activity in prostate cancer xenograft

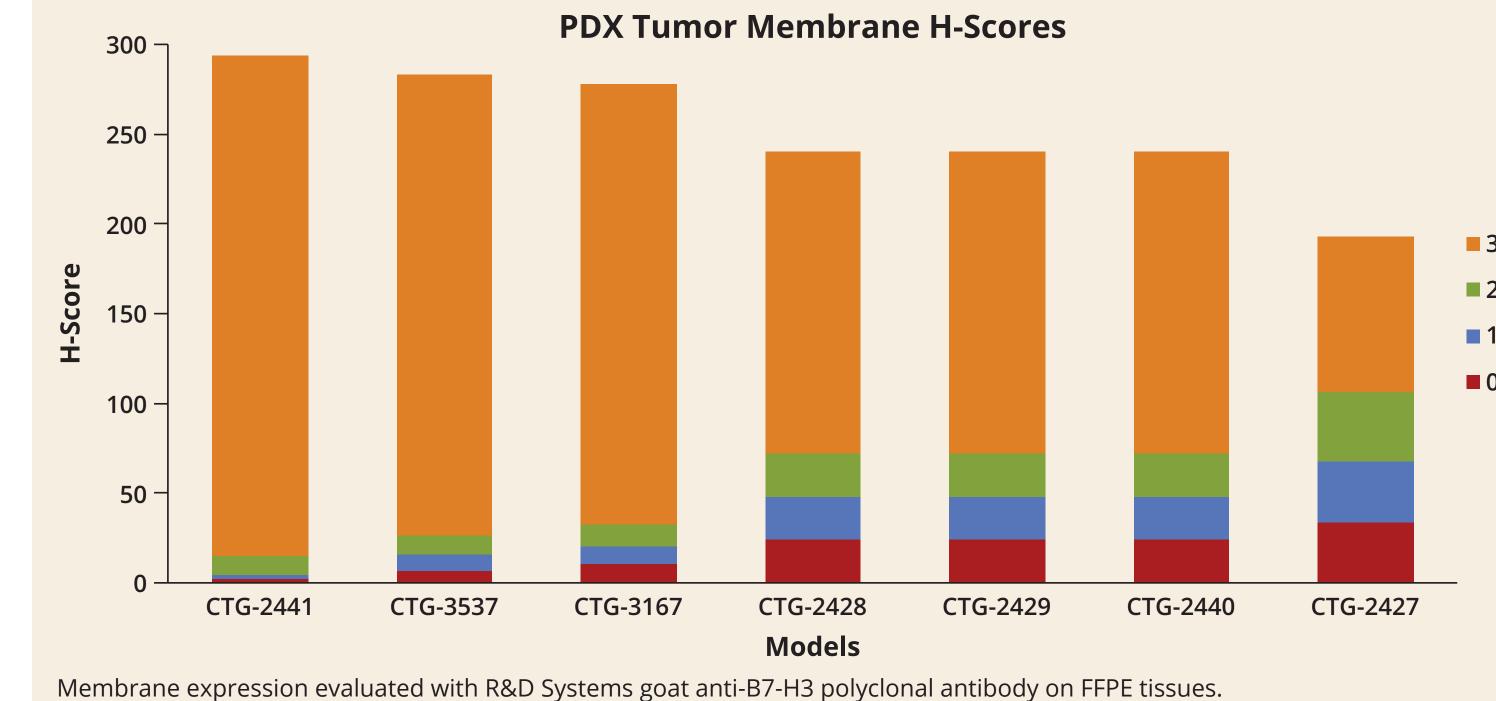
MGC018 was well tolerated in all models, with no impact on body weight

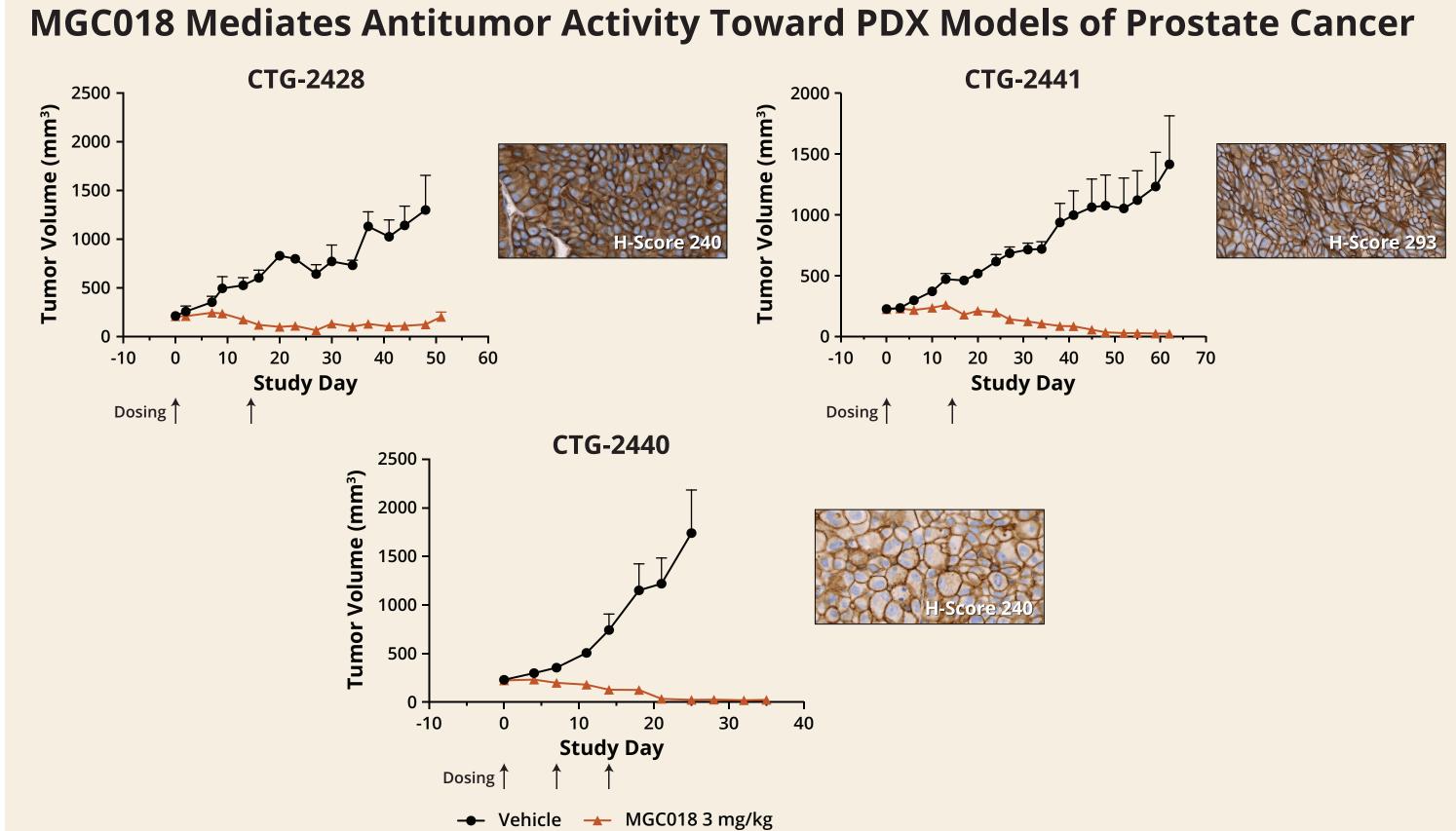
Antitumor Activity with MGC018 in Prostate Cancer PDX Models Prostate PDX Model Characteristics

PDX Model	Tumor Status	Harvest Site	Histology	Disease Stage	Treatment History	H-Score
CTG-2441	Metastatic	Bone	Adenocarcinoma	IV	Pretreated	293
CTG-3537	Metastatic	Bone	Adenocarcinoma	IV	Pretreated	283
CTG-3167	Metastatic	Circulating tumor cells	Adenocarcinoma	IV	Pretreated	277
CTG-2428	Metastatic	Bone	Adenocarcinoma	III	Pretreated	240
CTG-2429	Metastatic	Bone	Carcinoma	N/A	Pretreated	240
CTG-2440	Metastatic	Bone	Adenocarcinoma	N/A	Pretreated	240
CTG-2427	Metastatic	Bone	Adenocarcinoma	III	Pretreated	193

B7-H3 Tumor Expression Is Recapitulated in PDX Models of Prostate Cancer

PDX studies performed by Champions Oncology. H-Score represents average B7-H3 membrane staining.

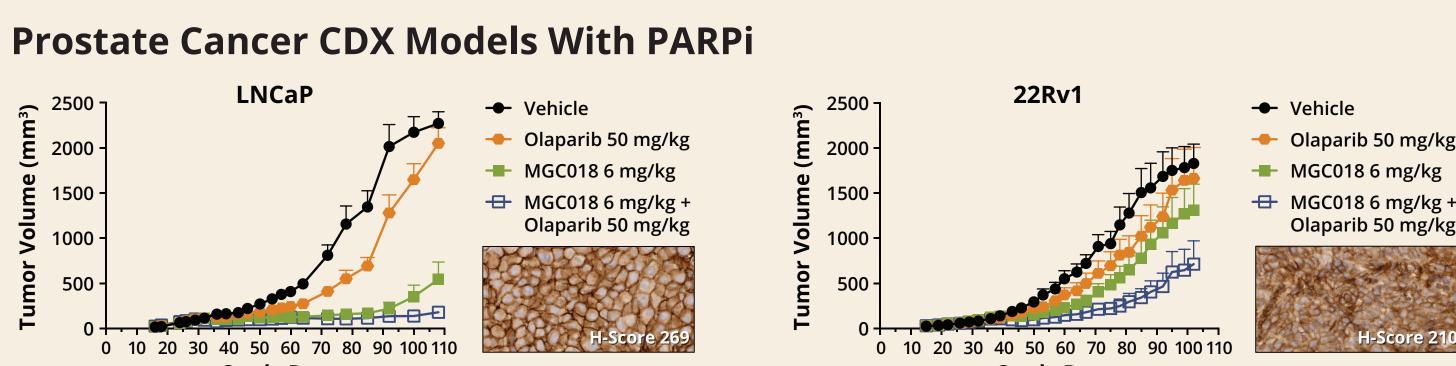




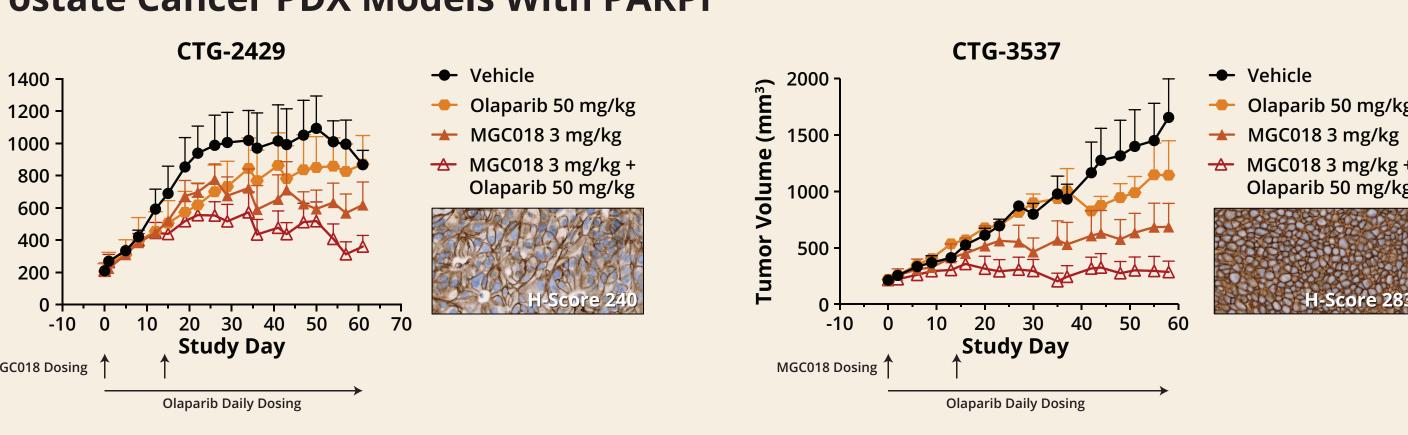
Enhanced Cytotoxicity with Combination of MGC018 and PARPi MGC018 Concentration (pM)

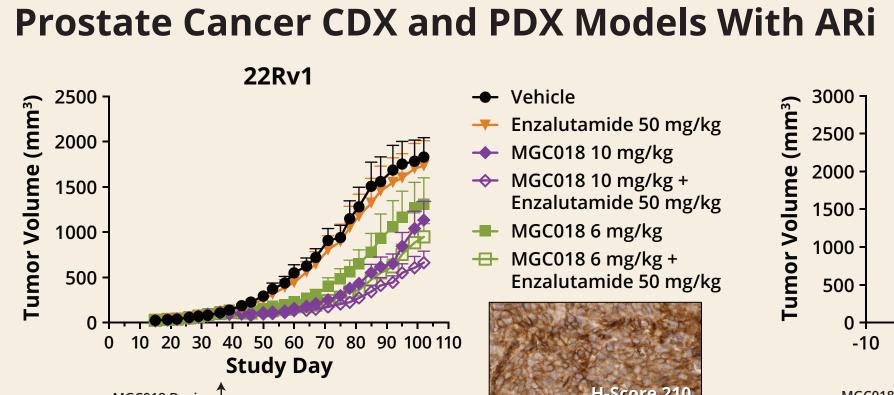
 MGC018 in combination with olaparib or niraparib increases cytotoxicity in prostate cancer cell lines

Enhanced Antitumor Activity with Combination of MGC018 and PARPi and ARi

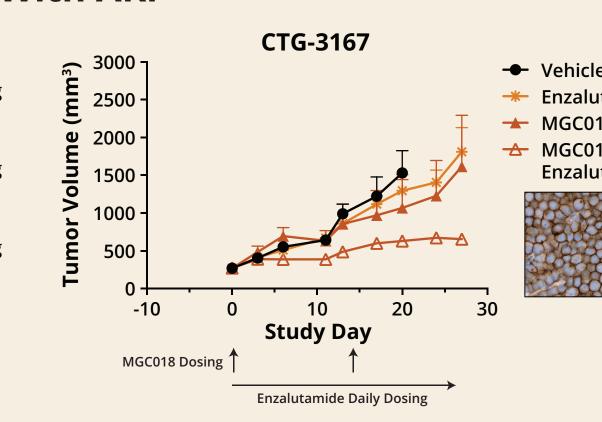


Prostate Cancer PDX Models With PARPi





(NCT03729596)



Conclusions

- B7-H3 is frequently overexpressed in prostate cancer –85% of primary prostate tumor 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 cell lines and enhanced activity in some lines when combined with inhibitors of PARP or AR
- MGC018 mediated apoptosis and induced markers of immunological cell death – Caspase 3/7 activation, PARP cleavage, calreticulin translocation, HMGB1 and ATP secretion
- 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 PARP or AR These results support B7-H3-directed ADC-based treatment of prostate cancer

with MGC018 A MGC018 phase 1/2 clinical study in advanced solid cancers is in progress

Reference

1. American Cancer Society's publication, Cancer Facts & Figures 2021, and the National Cancer Institute.

Acknowledgements

DUBA linker payload conjugated by and licensed from Byondis B.V., Nijmegen, the Netherlands.