Preclinical Development of a Probody Drug Conjugate (PDC) Targeting CD71 for the Treatment of Multiple Cancers

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ABSTRACT

The target of Probody Drug Conjugates (PDCs) have typically been selected to provide therapeutic advantage to molecules that are highly expressed in tumors but are low or absent in normal tissues. The creation of a probody CD71 target engaging these requirements is limited. either because expression in tumors is not high enough for optimal efficacy or because expression in normal tissues is too high, leading to toxicity. CDs are antibodies designed to present a toxic payload posttranslationally activated in the tumor microenvironment. Probody technology allows for the presentation of a stable probody antigen-targeting tandem, which remains in a modified antigen form until activated in normal tissues. The CD71 Probody produced potent single-agent efficacy and cures in a lung cancer xenograft model. The conjugate was well tolerated, which was consistent with previous observations in normal tissue xenografts. We have demonstrated that we can_IMG16_364534076.png

INTRODUCTION

Probody Therapeutics are Designed to Bind to Tumors & Protect Healthy Tissue

Hematologic ProFile

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

Toxicology

- Distributed activity of split antibody
- Can be engineered to maintain Probody therapeutic linkage

Substrate Linker

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

Probody Drug Conjugates are Designed to Target a Densely Concentrated Tumor Antigen, Regardless of Expression on Normal Tissue

Probody

ADC

PDC

Overexposed Properties

Expression in healthy tissue
Low
Low or High

Expression in tumor
High
High

Resulting Properties

Adequately exposed
Often Exposed

Tumor type addressed
One-Flow
High

Proprotein can cancer type
Low
Very High

Figure 1: Comparable Binding by Antibody to Human & Cynomolgus CD71

Figure 2: Patient in vitro Cytotoxicity of CD71 ADC in Multiple Tumor Cell Types

Figure 3: CD71 is Highly Expressed in Many Metastatic Cancers

Figure 4: CD71 PDC Renders Complete and Durable Responses in Human Xenograft Tumors At Or Below Clinically Relevant Doses

Figure 5: CD71 PDC is Effective in In Multiple COK and PDX models

Figure 6: CD71 Probody Therapeutic Shows Extended Exposure in Cynomolgous Monkeys, Consistent with Reduced Binding in Normal Tissues

Figure 7: CD71 PDC Safety in Cynomolgus Monkeys at a Clinically Relevant Dose

RESULTS

TARGETING CD71

In a CD71 expressing hematopoietic precursor cell line, we observed a 25% reduction of CD71

In normal tissue xenografts, we observed a 25% reduction of CD71

In hematologic precursors and other normal tissues

Further, we observed the development of Probody therapeutics that are effective against cancers with various levels of CD71 expression in both tumors and normal tissues

SUMMARY/CONCLUSIONS

PDCs have the potential to safely target highly expressed tumor antigens, regardless of expression on normal tissue, thus expanding the utility of ADCs for tumors

We have developed a PDC targeting CD71, a highly expressed antigen present in many cancers but also in hematologic or normal tissues

CD71 PDC is efficacious in cell line-derived and patient-derived xenograft tumors at doses equal to or below the predicated clinical therapeutic dose

In monkeys, CD71 PDC protects against leukopenia and severe toxicity associated with its ADC

CD71 Probody PK is consistent with protection from binding to normal monkey tissue sink

The safety and efficacy profiles of CD71 PDC are supportive of further development