Affinity tuned Xmab® 2+1 PSMA x CD3 bispecific antibodies demonstrate selective activity in prostate cancer models

Alex Nishal, Matthew Dragovich, Erik Pong, Veronica Zeng, Christine Bonzon, Kendra N. Avery, Rumana Rashid, Connie Ardila, Bjorn Millard, Alison Betts, Umesh S. Muchhal, Gregory L. Moore, Michael Hedvat, Seung Y. Chu, and John R. Desjarlais

Introduction

- Prostate specific membrane antigen (PSMA) is an intriguing prostate cancer (PC) target as its expression can increase in higher grade tumors, metastasis, and with androgen deprivation therapy.
- Type II integral membrane protein, PSMA has long generated interest as a potential therapeutic target.
- Normal cell expression of PSMA has been described on the secretory epithelium of prostate tissues, small intestine, proximal renal tubules, and salivary glands.
- To create a more selective T-cell engaging antibody for PC, we extended our Xmab heterodimeric Fc platform to create the 2+1 Fab-scFv-Fc format, which is bivalent for PSMA and monovalent for CD3.

Cell line proxies for “on-target” and “off-target” tissue identified by IHC

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<tr>
<th></th>
<th>High</th>
<th>Med</th>
<th>Low</th>
<th>Absent</th>
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</thead>
<tbody>
<tr>
<td>Prostate Cancer</td>
<td>160%</td>
<td>55%</td>
<td>28%</td>
<td>14%</td>
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<tr>
<td>Normal Tissue</td>
<td>3%</td>
<td>6%</td>
<td>7%</td>
<td>18%</td>
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</tbody>
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- PSMA prevalence was measured by IHC scoring of 160 PC and 93 normal tissue FFPE cones.
- PC3 cells were stably transduced and sorted to create a gradient of PSMA-expressing lines for downstream studies.
- Antibody/cell on various cell lines ranged from ~140K to ~3K, and were correlated against tumor and normal tissues by IHC.

On-target

- Cell line proxies for “on-target” and “off-target” tissue identified by IHC

Off-target

- Cell lines incubated with T cells for 24 hr at E:T of 1:1, then incubated with antibodies for 48 hr and assayed for luminescence.
- T cell activation markers such as Ki67 mirror the selectivity of the 2+1 bispecifics.

Summary

- Tuned 2+1 bispecifics selectively kill high expressing cell lines in vitro.
- Monovalent, off-target and low expressing tissue affinity.
- Sensitive and selective to PSMA vs CD3.
- Off target reactivity is low.

Bivalent 2+1 format retains binding despite reduced monovalent affinity

- Favorable solution properties (SEC).
- High purity bispecific (IEX).

Modeling predicts tumor-selective killing under clinical conditions

- Semi-mechanistic model of tumor formation (T cell, bispecific antibody, tumor cell).
- Assumed in vivo conditions for “cold” prostate tumors (E:T 1:100).
- Tuned 2+1 bispecifics selectively kill high expressing cell lines in vitro.
- Not selective vs Reduced CD3 affinity.
- Increasing Selectivity.

Xmab 2+1 bispecifics reverse tumor growth of "on-target" cell line in mice

- PBS.
- αPD-1 mAb.
- PSMA affinity x Reduced CD3 affinity.

Tuned 2+1 bispecifics selectively kill high expressing cell lines in vitro

- Not selective vs Reduced CD3 affinity.
- Increasing Selectivity.

Tuned Xmab 2+1 PSMA x CD3 bispecific antibodies:

- Are humanized, well-behaved, and efficiently purified and manufactured.
- Feature a human Fc domain, which can be modified with Xtend technology.
- Effectively recruit T cells to kill PSMA+ cancer cell lines in vitro.
- Induce anti-tumor activity in human PBMC-engrafted NSG mice.
- Are predicted to have strong anti-tumor activity with an improved safety profile.

These results support clinical testing of a 2+1 PSMA x CD3 bispecific antibody as a therapeutic option for patients with prostate cancer.

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Contact: jds@xencor.com