HPN601 Is A Protease-Activated EpCAM-Targeting T Cell Engager with an Improved Safety Profile for the Treatment of Solid Tumors

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Harpoon Therapeutics, Inc.
South San Francisco, CA
November 12, 2020
Disclosure

• All authors are current or former employees and are shareholders of Harpoon Therapeutics
The Need for a Conditionally Active T Cell Engager Prodrug To Target More Broadly Expressed Tumor Antigens

PROBLEM:

• T cell engagers are potent, but limited to tumor antigens with restricted normal tissue expression
• Many solid tumor antigens have normal tissue expression liabilities
• Several T cell engager targets have encountered dose-limiting toxicities in the clinic
  • Examples: EpCAM, gpA33, B7-H3, CEACAM5

SOLUTION:

• Design a T cell engager prodrug that is active in tumor and spares normal tissues
• Enables targeting of more solid tumor antigens
ProTriTAC is a T cell engager prodrug platform based on Harpoon’s clinically validated TriTAC components.

**TriTAC**
- αTarget
- αALB
- αCD3

**ProTriTAC**
- αTarget
- αALB
- αCD3

*Started with same TriTAC binders*
*Rearranged binders*
*Added protease linker and masking moiety*
ProTriTAC Links Masking with Half-Life Extension To Improve the Therapeutic Index (TI)

- **Long-lived prodrug**
- **Activation by tumor proteases & T cell-directed killing**
- **Rapid clearance in circulation**

**CIRCULATION**
- αALB
- αCD3
- αTarget

**TUMOR**

**CIRCULATION**

![Diagram showing the process of ProTriTAC](image-url)
EpCAM Is a Broadly Expressed Epithelial Tumor Antigen

• **Epithelial Cell Adhesion Molecule (EpCAM, CD326)**

• Highly expressed on many solid tumors\(^1\)

• Marker for circulating tumor cells\(^2\)

• Therapeutic potential hindered by its normal tissue expression

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Efficacy of Past EpCAM T Cell Engagers Was Limited Because of On-Target Toxicity in Normal Tissues

<table>
<thead>
<tr>
<th>T Cell Engager</th>
<th>Route of Admin.</th>
<th>Clinical Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitomab</td>
<td>Systemic (intravenous)</td>
<td>MTD = 24 µg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical activity noted at dose levels 2-4x above MTD&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Catumaxomab</td>
<td>Local (intraperitoneal)</td>
<td>Approved for malignant ascites in Europe&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not tolerated as systemic therapy&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

- Systemic administration not tolerated, but highest (non-tolerated) doses for solitomab had clinical activity
- Local administration had more success, but cannot target all metastatic tumors

**Goal of EpCAM ProTriTAC** = systemic administration + local activity in all tumors

Two EpCAM-Specific Binders Were Chosen for Further Efficacy and Toxicity Assessments In Vivo

- Comparable masking observed in functional T cell killing (TDCC) assays
- ProTriTAC with the mouse cross-reactive binder used for TI assessment
EpCAM ProTriTAC Is 3x Less Potent than the Tool TriTAC in Shrinking LoVo Colon Tumors in Mice
EpCAM ProTriTAC is 30x Safer than the Tool TriTAC in the Same Tumor-Bearing Mice

Survival:

Clinical Chemistry:

- **ALT**: 
  - >30x

- **AST**: 
  - >30x

- **Bilirubin (Total)**: 
  - 30x
The 30x Improved Safety of EpCAM ProTriTAC Is Further Supported by Mouse Histopathology in the Same Tumor-Bearing Mice

ProTriTAC enables better discrimination of tumor vs. normal tissue to reduce on-target tissue damage

### Mouse Liver Histopathology Findings

<table>
<thead>
<tr>
<th>Dose level (mg/kg)</th>
<th>Ctrl</th>
<th>TriTAC</th>
<th>ProTriTAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>0.003</td>
<td>0.01</td>
<td>0.03 0.1 0.3</td>
</tr>
<tr>
<td>Coagulation necrosis</td>
<td>-</td>
<td>-</td>
<td>100% 100%</td>
</tr>
<tr>
<td>Portal fibrosis</td>
<td>10%*</td>
<td>10%*</td>
<td>100% 100%</td>
</tr>
<tr>
<td>Bile ductule dilation</td>
<td>-</td>
<td>-</td>
<td>100% 100%</td>
</tr>
</tbody>
</table>

Note: percentages represent proportion of animals with the finding, asterisks denote findings were all of minimal severity.

### Mouse Liver Sections (H&E stain)

ProTriTAC 0.3 mg/kg

TriTAC 0.3 mg/kg
10x Therapeutic Index Expansion Achieved for ProTriTAC in a Tumor Xenograft Model in Mice

<table>
<thead>
<tr>
<th></th>
<th>Minimum Efficacious Dose</th>
<th>Maximum Tolerated Dose</th>
<th>Therapeutic Index (TI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TriTAC</td>
<td>0.03 mg/kg</td>
<td>0.03 mg/kg</td>
<td>1</td>
</tr>
<tr>
<td>ProTriTAC</td>
<td>0.1 mg/kg</td>
<td>1 mg/kg</td>
<td>10</td>
</tr>
</tbody>
</table>

ProTriTAC Advantage 10x

- **TI expansion demonstrated in vivo**: efficacy + tox in the same animal
- **Preclinical model validated**: similar on-target tox in mouse and in human \(^1\)

1. Kebenko, OncoImmunol 2018
EpCAM ProTriTAC with the Clinical Candidate Binder (HPN601) Confirms TI Improvement by Comparing Across Species

Better Efficacy in Mouse

Established HT29 Tumor Xenograft Model

Tumor volume, mm$^3$

Day, post tumor implantation

Control

TriTAC

ProTriTAC (HPN601)

Both TriTAC and ProTriTAC dosed at 100 µg/kg

Better Safety in Cyno

Peak Cytokine Levels

Cytokines (pg/ml)

TriTAC

ProTriTAC (HPN601)

Both TriTAC and ProTriTAC dosed at 30 µg/kg
HPN601 Is Active in Multiple Established Tumor Xenograft Models

Demonstrates anti-tumor activity and prodrug processing in multiple tumor types
Summary

• ProTriTAC is a new approach to engineer conditionally active T cell engager prodrugs

• HPN601 is an EpCAM-targeting ProTriTAC

• 10x improved TI compared to a constitutively active T cell engager

• Efficacious in multiple EpCAM-expressing xenograft tumor models in vivo

• IND-enabling studies initiated
Acknowledgements

Translational Medicine
• Che-Leung Law
• Laurie Tatalick
• Vaishnavi Ganti

CMC
• Susan Dana Jones
• Alpana Naresh
• Mark Wesson

We thank all other Harpoon staff members who enabled this effort.