Redirecting T Cells for Prostate Cancer Immunotherapy

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COI/Disclosures

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Equity
Actym, Allector, Atreca, Bioalta, Bolt, Keyhole, Immunogenensis, Nutcracker, RAPT, Scribe, Senti, Soteria, TeneoBio
Immunotherapeutic approaches

**Enhancing endogenous immunity**
- Blocking inhibitors
- Stimulating effectors
  - Vaccines
  - Immune checkpoint modulators

**Redirecting immune effectors**
- Engineering cellular specificities
- Colocalizing effectors to tumors
  - T cell engagers
  - CART

**PSMA**
**PSCA**
**STEAP**
**B7-H3**
PSMA trispecific: AMG 160

- **BiTE®** molecules engage a patient’s own T cells to attack and eradicate cancer cells:\(^1\)
  - T-cell activation induces transient cytokine release and tumor killing:\(^1\)
- **Blinatumomab (BLINCYTO®, Amgen Inc.)** is the first and only bispecific immunotherapy approved in oncology worldwide:\(^1\)
- **AMG 160** is a half-life extended PSMA x CD3 BiTE® immunotherapy for mCRPC
AMG160: Adverse events

- 43 patients received ≥ 1 dose of AMG 160 monotherapy
  - 41 (95.3%) patients experienced TEAEs
  - 19 (44.2%) patients remained on AMG 160 at the time of data analysis
    - 6 (14.0%) received treatment ≥ 6 months

**TRAEs**
- 41 (95.3%) patients experienced TRAEs
  - No grade 5 events, and none resulted in treatment discontinuation
- 3 reversible dose-limiting toxicities occurred
  - Grade 3 rash (n = 2)
  - Grade 3 GI hemorrhage (n = 1)

**ADAs**
- 6 of 30 (20.0%) patients assessed developed ADAs affecting drug exposure between cycles 1 and 10
  - No AEs associated with ADAs were observed

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**TRAEs in ≥ 20% of patients (N = 43)***

<table>
<thead>
<tr>
<th>TRAE, n (%)</th>
<th>All Grade, n (%)</th>
<th>Grade 3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS (Lee criteria)^†</td>
<td>39 (90.7)</td>
<td>11 (25.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (44.2)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Vomiting^†</td>
<td>19 (44.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nausea^†</td>
<td>17 (39.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pyrexia^†</td>
<td>16 (37.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Headache^†</td>
<td>15 (34.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhoea^†</td>
<td>14 (32.6)</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>13 (30.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rash^†</td>
<td>12 (27.9)</td>
<td>4 (9.3)</td>
</tr>
<tr>
<td>Hypophosphataemia</td>
<td>11 (25.6)</td>
<td>4 (9.3)</td>
</tr>
<tr>
<td>Hypotension^†</td>
<td>10 (23.3)</td>
<td>5 (11.6)</td>
</tr>
<tr>
<td>Chills^†</td>
<td>10 (23.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>10 (23.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>9 (20.9)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* 8 patients experienced grade 4 laboratory abnormalities that were clinically non-significant; ^† CRS-related
AMG160: PSA modulation

- PSA reductions (best response) were dose dependent and occurred in 24/35 (68.6%) evaluable patients (20 July 2020)
- PSA reductions > 50% occurred in 12/35 (34.3%) evaluable patients
AMG 160: Clinical responses

Patient: 10112001002
Prior Rx: Surgery, radiotherapy, docetaxel, enzalutamide, bicalutamide, and talazoparib
Cohort: 4 (0.09 mg with cycle 1 priming)

Patient: 10166004005
Prior Rx: Surgery, docetaxel, enzalutamide, sipuleucel
Cohort: 4 (0.09 mg with optimised cycle 1 priming)

Patient: 10166004006
Prior Rx: Radiotherapy, apalutamide, docetaxel, sipuleucel-T, radium-223
Cohort: 5 (0.3 mg with optimised cycle 1 priming)

PR by 3 Months
PSMA PET/CT

Baseline
Week 12

Not RECIST evaluable
PSMA PET/CT

Baseline
Week 12

PR (u) by 2.5 Months

Baseline
T01 Liver
Segment VIII
Week 10
40% reduction
vs baseline

Rapid PSA Drop in 1 Month

Best PSA reduction: -98.1%

Days on Treatment

Rapid PSA Drop in 1 Month

Best PSA reduction: -87.9%

Days on Treatment

Rapid PSA Reduction

Best PSA reduction: -75.5%

Days on Treatment

Tran et al. ESMO 2020
PSMA “Trispecific”: HPN424

- Constructed as a small, globular protein (~50kDa)
- Binds monovalently to CD3 and PSMA

Bendell, Fong et al. ASCO 2020
Trial Schema

Part 1 – Dose Escalation

Dose Escalation: Single Patient

≥ Gr 2 study drug related toxicity

Fixed Dose Escalation: 3 + 3 (3 – 6 pts per dose level)

Step Dosing
Dose Escalation: 3 + 3 (3 – 6 pts per dose level)

Maximum Tolerated Dose (MTD) or Recommended Phase 2 Dose (RP2D)

Part 2 – Dose Expansion

20 pts treated at RP2D determined in Part 1

• Target Population
  - Disease progression on the prior systemic regimen
  - At least two prior systemic therapies approved for mCRPC
  - Prior chemotherapy allowed, but not required

• Trial Design
  - Objectives include characterization of safety, PK, pharmacodynamics and identification of expansion dose
  - Tumor assessments performed q9w and include conventional CT and bone scans and PSA

• Dosing, Administration & Exposure
  - HPN424 administered qw, 1 hour IV infusion (one cycle = 3 weeks)
  - Starting dose of 1.3ng/kg established by minimally anticipated biological effect level

DeBono, Fong et al. ASCO 2021
# Baseline Demographics

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>70</td>
<td>43 - 91</td>
</tr>
<tr>
<td>Black</td>
<td>8 (9%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td>Other / Not reported</td>
<td>10 (11%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time Since Diagnosis (Years)</th>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>69 (78%)</td>
<td>37 (49%)</td>
<td>38 (51%)</td>
</tr>
<tr>
<td>Black</td>
<td>8 (9%)</td>
<td>50 (56%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other / Not reported</td>
<td>10 (11%)</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ECOG Performance Status</th>
<th>0</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>39 (44%)</td>
<td>50 (56%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PSA (ng/mL)</th>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Prior Therapy</td>
<td>89 (100%)</td>
<td>5 (1 – 12)</td>
<td></td>
</tr>
<tr>
<td>Novel Hormonal Therapy</td>
<td>87 (98%)</td>
<td>2 (0 – 4)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy (mCRPC)</td>
<td>65 (73%)</td>
<td>1 (0 – 3)</td>
<td></td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>30 (33%)</td>
<td>0 (0 – 3)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of Metastases</th>
<th>Bone</th>
<th>Lymph Node</th>
<th>Lung</th>
<th>Liver</th>
<th>Other Visceral</th>
<th>Other Non-visceral</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA Progression</td>
<td>27 (42%)</td>
<td>3 (5%)</td>
<td>10 (16%)</td>
<td>24 (38%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA &amp; Clinical Progression</td>
<td>10 (16%)</td>
<td>3 (5%)</td>
<td>10 (16%)</td>
<td>24 (38%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA &amp; Radiographic Progression</td>
<td>24 (38%)</td>
<td>10 (16%)</td>
<td>10 (16%)</td>
<td>24 (38%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Actual n is indicated where full dataset not available
Pharmacokinetics

- Dose proportional increase in \( C_{\text{max}} \)
- Mean \( T_{1/2} \) with dose group of \( N>2 \) is 24 hrs (range of 9 – 70 hrs)
- PK parameters: \( T_{1/2}, \text{CL}, \) and volume of distribution are dose independent suggesting linear PK kinetics

DeBono, Fong et al. ASCO 2021
Adverse Events

- Maximum-tolerated dose (MTD) not yet reached

- Dose Limiting Toxicities (DLTs):
  - Observed at doses ranging from 96 to 300ng/kg
  - Did not limit escalation
  - Most Common: Transaminitis G4 (n=6); Cytokine Release Syndrome G3 (n=4)
    - Majority of events occur with first dose

- No Grade 4 or 5 CRS, no Grade 5 treatment-related AEs

- Two of 89 (2%) pts discontinued treatment due to treatment-related AEs

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<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>All Grades</th>
<th>Grade 3+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytokine-Related AEs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytokine Release Syndrome (CRS)</td>
<td>61 (69%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Chills</td>
<td>60 (67%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>58 (65%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>35 (39%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Infusion Related Reaction (IRR)</td>
<td>20 (22%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Flushing</td>
<td>13 (15%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>11 (12%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td><strong>Liver Function Tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST Increase</td>
<td>28 (31%)</td>
<td>19 (21%)</td>
</tr>
<tr>
<td>ALT Increase</td>
<td>26 (29%)</td>
<td>14 (16%)</td>
</tr>
<tr>
<td><strong>Other Adverse Events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>45 (51%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>40 (45%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>34 (38%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>28 (31%)</td>
<td>10 (11%)</td>
</tr>
<tr>
<td>Headache</td>
<td>24 (27%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>21 (24%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>20 (22%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>20 (22%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>20 (22%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

* Includes AEs that were reported as concurrent symptoms of the CRS events

b CRS Grading according to ASTCT 2019 criteria

DeBono, Fong et al. ASCO 2021
HPN424 Clinical Activity

Time on Treatment Target Dose >96ng/kg Cohorts

Weeks

DeBono, Fong et al. ASCO 2021
• Initiated HPN424 at 160ng/kg
• Demonstrated RECIST partial response (-32%) at 1st post-baseline scan (Week 9), confirmed PR (-43%) at Week 18, response maintained at Week 36
• Remains on study after 41 weeks of treatment
HPN424-1001 Summary

• HPN424, a novel half-life extended PSMA-targeting T cell engager, is active and generally well tolerated.

• CRS has been transient and manageable with 4% of patients experiencing Grade 3 CRS, no Grade 4 or 5.

• CRS and transaminitis events observed most often in Cycle 1, with diminished frequency and severity in subsequent cycles.

• HPN424 has antitumor activity including a confirmed PR per RECIST, PSA declines and CTC reductions.

• Treatment duration > 24 weeks observed in 15 of 74 (20%) pts, including 8 of 17 (47%) chemo-naïve patients.

• Assessment of optimal target dose and patient population for expansion ongoing.
How can we improve the therapeutic index of these T cell engagers?

• The majority of the T cell engagers in development use an anti-CD3 from: SP34, OKT3, UCHT1.

  All high affinity…

• Could lower affinity anti-CD3 domains reduce toxicity without compromising efficacy?
Development of TNB-585

Activating αCD3 Ab
- Retained Efficacy, Reduced Cytokine Secretion
- Reduced Treg activation
- Unique CD3 δε epitope

αPSMA UniAb
- High affinity
- Heavy chain only

Fc Tail
- Silenced human IgG4 Fc
- Engineered to prevent arm exchange
- Knob/Hole design
- No off-target T-cell activation

Dang et al. PCF 2019
TNB-585 activates T cells \textit{in vitro}

PSMA+: LN-CAP, 22Rv1
PSMA-: DU145

Positive Control: OKT3-like

T cell/tumor/drug cocultures

Dang … Fong, Dalvi. JITC 2021
TNB-585 attenuates cytokine production

Dang … Fong, Dalvi. JITC 2021
TNB-585 induces tumor regression *in vivo*

Dang ... Fong, Dalvi. JITC 2021
TNB-585 induces tumor regression *in vivo*

Dang ... Fong, Dalvi. JITC 2021
Conclusions

• Attenuating the affinity of the anti-CD3 binding domain of T cell engagers may allow for:
  • Maintenance of anti-tumor efficacy
  • Reduction in cytokine release and potential for toxicities

• The clinical trial is now accruing…
Take-home

• PSMA targeting T cell engagers are showing early signs of clinical activity, but with toxicities.
• Dosing and premedication with steroids are being used to ameliorate these toxicities.
• Stay tuned for clinical data from multiple novel T cell engagers targeting PSMA.
• This is just targeting PSMA…
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Patients and their families