Efficacy and safety of P-BCMA-101 CAR-T cells in patients with relapsed/refractory (r/r) multiple myeloma (MM)


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Not All T-Cells are Created Equally: 
The Importance of Stem Cell Memory T Cells ($T_{SCM}$)

Products with High % of $T_{SCM}$ Cells:
- Associated with best clinical responses
- More gradual tumor killing with less toxicity
- Key to CAR-T success in solid tumors
- Better duration of response
- Potential for re-response

**THE POTENTIAL BENEFITS**

- Self renewing
- Long lived
- Multipotent
P-BCMA-101 is a Novel CAR-T Cell Made With Transposons (piggyBac®)

**Very Large Cargo Capacity:**
Potentially >20x Lentivirus

- **piggyBac DNA Transposon**
- **piggyBac RNA Transposase**

- **Genomic DNA**
  - “Cut” to insert cargo
  - “Paste” to integrate DNA

Large transgene with ability to carry multiple CAR or TCR molecule genes and armoring technology

**Designed To Have Desirable Product Attributes**

**INCORPORATES PROPRIETARY SAFETY SWITCH**
- Rapid, dose-dependent elimination of CAR-T cells with rimiducid if needed
- Potential management of Cytokine Release Syndrome (CRS) or other AEs

**DIFFERENTIATED BINDING CAR-T MOLECULE**
- Centyrin™ molecule with high-specificity binding to BCMA
- Fully human with no tonic signaling observed to date

**DRUG RESISTANCE GENE PERMITS POSITIVE SELECTION**
- ~100% of T-cells in final product express the CAR molecule
- Predicted to result in greater therapeutic index
Cell-based products are living drugs and are affected by donor and manufacturing variability. The type and quality of cells affect product performance.

Improving transposition frequency during manufacturing may improve final product:

- More CAR+ cells, less cell proliferation and cell death in culture means healthier more proliferative cells in a patient.

Improving Transposition of P-BCMA-101 with a Modified Manufacturing Process with Nanoplasmid (NP):

- Reduces the backbone size to < 500 bp (less DNA = less toxicity) vs. >2000 bp for Standard Plasmid.
- Brings piggyBac® ITRs closer together (enhanced transposition efficiency).

Incorporated manufacturing changes that increased transposition frequency (2-fold) in the Phase 1 trial.
Open Label, 3+3 Design, up to 120 patients, multiple exploratory cohorts

Key eligibility criteria:
- RRMM
- ECOG PS 0-1
- ≥3 prior lines (PI+IMID)
- ≥2 prior lines if refractory to both PI+IMID
- Prior anti-BCMA or CAR-T cell therapy allowed

Single administration (SA)

Cyclic administration - dose divided A) 1/3+2/3 or B) 1/3+1/3+1/3

Combination Administration
- Cohort R: lenalidomide 10-25mg PO QD 21/28d
- Cohort RP: lenalidomide 10-25mg PO QD 21/28d
- Cohort RIT: rituximab 375 mg/m² via IV infusion day -12, -5, and q8w post-CART
### Baseline Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th>Parameter (n=55)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (min, max) age, y</td>
<td>60 (42, 74)</td>
</tr>
<tr>
<td>Male:Female, n (%)</td>
<td>37 (67):18 (33)</td>
</tr>
<tr>
<td>Median (min, max) time since diagnosis, y</td>
<td>4.9 (0.9, 13.9)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>20 (36)</td>
</tr>
<tr>
<td>1</td>
<td>35 (64)</td>
</tr>
<tr>
<td>Median (min, max) prior lines of therapy</td>
<td>8 (2, 18)</td>
</tr>
<tr>
<td>Proteasome inhibitor, n (%)</td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td>53 (96)</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>47 (85)</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>15 (27)</td>
</tr>
<tr>
<td>IMiD, n (%)</td>
<td>55 (100)</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>55 (100)</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>50 (91)</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>12 (22)</td>
</tr>
<tr>
<td>Daratumumab, n (%)</td>
<td>51 (93)</td>
</tr>
<tr>
<td>Triple Class (PI, IMiD and anti-CD38), n (%)</td>
<td>51 (93)</td>
</tr>
<tr>
<td>anti-BCMA, n (%)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Prior autologous SCT</td>
<td>37 (67)</td>
</tr>
</tbody>
</table>
Safety: Adverse Events of Interest

### TEAE, n (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Overall (n=53)</th>
<th>≥ Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Limiting Toxicity (DLT)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Cytokine Release Syndrome</td>
<td>9 (17.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Administered tocilizumab</td>
<td>4 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Administered steroids</td>
<td>3 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>2 (3.8)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>24 (45.3)</td>
<td>10 (18.9)</td>
</tr>
<tr>
<td>First month</td>
<td>9 (17.0)</td>
<td>4 (7.5)</td>
</tr>
<tr>
<td>Neutropenia/Neutrophil count decreased</td>
<td>41 (77.4)</td>
<td>40 (75.5)</td>
</tr>
<tr>
<td>Thrombocytopenia/Platelet count decreased</td>
<td>22 (41.5)</td>
<td>16 (30.2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>21 (39.6)</td>
<td>16 (30.2)</td>
</tr>
<tr>
<td>White Blood Cell Count Decreased</td>
<td>21 (39.6)</td>
<td>19 (35.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (32.1)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Highest incidence TEAE were infection, neutropenia, thrombocytopenia, anemia, leukopenia and fatigue
No rimiducid use or ICU admission for CRS
16 patients treated outpatient

#### Cytokine Release Syndrome by Dose Level (n = 53)

All CRS was Grade 1/2
No CRS in RIT/R/RP groups.
CRS in 1/4 patients in cyclic dosing groups (1/2 NP)
Data cutoff: November 11th, 2020. ORR, objective response rate, attaining sCR (inc. MRD-), CR, VGPR or PR, including confirmed and unconfirmed responses. Evaluable patients: evaluable first response assessment by IMWG m-protein criteria or PD/death.
The percentage (fraction) of a P-BCMA-101 CAR-T cell dose that were T$_{SCM}$ correlated with the probability of response by IMWG criteria
Correlations Between Cmax/AUC and Response

The Cmax and AUC of P-BCMA-101 expansion assessed by PCR in peripheral blood correlated with the probability of response by IMWG criteria.

The Cmax and AUC of P-BCMA-101 expansion assessed by PCR in peripheral blood correlated with the probability of response by IMWG criteria.
Initial Dose Escalation with Nanoplasmid (NP) Manufacturing Process: Equal Safety and Better Response Compared to Standard Plasmid

- **P-BCMA-101 with Nanoplasmid demonstrated higher ORR** than P-BCMA-101 with standard plasmid
  - 66.7% vs 50% by IMWG
- **P-BCMA-101 Nanoplasmid delivered deeper responses** than P-BCMA-101
  - 3 P-BCMA-101 Nanoplasmid patients at VGPR or CR compared to zero for standard plasmid
- **Safety profile** was preserved with one Grade 1 CRS observed with either product in these patients

**ORR** for cyclic dosing was 1/4 (PR). Cmax was low and followed individual administrations without expanding AUC.

*3 patients dosed but only 2 evaluable by IMWG criteria. 3rd patient had plasmacytomas and had significant response by PET scan.

Data cutoff: November 11th, 2020. ORR Objective Response Rate, attaining sCR, CR, VGPR or PR, including confirmed and unconfirmed responses. Evaluable patients: Obtained first response assessment by IMWG m-protein criteria or PD/death.
CAR-T Expansion is Associated with Best Responses

Patient 106-004: Long Term sCR
- 59 yo male with 5 prior lines
- Treated with P-BCMA-101 in August 2018
- Rapidly reached VGPR then sCR, continues on study at > 2 years
- Clinical evidence of engraftment and persistence of CAR+ cells at ~22 months

Patient 106-016: sCR recently treated with NP
- Patient: 69 yo female TP53mut with 4 prior lines
- Treated with P-BCMA-101 (NP) in June 2020
- Rapidly reached sCR
- Similar evidence of expansion and engraftment at early timepoints
Safety & Efficacy with a Novel BCMA CAR-T Cell Product

- Excellent safety and efficacy profile demonstrated in a standard dose escalation, doses up to ~1200 x 10^6 CAR-T cells
  - Very low rates of CRS (17%, no Grade 3+), CRES and usage of tocilizumab/steroids, no ICU admissions
    - May allow for greater patient access (e.g., administration at community hospitals and/or outpatient sites)
  - Early memory T cell phenotype (TSCM) may result in greater safety and efficacy

- Manufacturing matters, use of modified process may improve expansion and efficacy
  - PiggyBac with Nanoplasmid exemplifies continuous innovation in manufacturing
  - Current process at .75X10^6 dose results in 67% ORR, 50% VGPR/sCR with 12.5% CRS

- Preliminary results with novel dosing methods and combinations suggest unique outcomes
  - Safety profile is preserved with all strategies
  - Multiple doses do not appear to improve PK or efficacy, but increase logistical complexity
  - Rituximab and lenalidomide treated patient numbers are too low to assess differences at this time
  - Dose escalation is continuing in Nanoplasmid groups

Summary
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Thank You