SQZ-PBMC-HPV-101:

Preliminary results of a first-in-human, dose-escalation study of a cell-based vaccine in HLA A*02+ patients with recurrent, locally advanced, or metastatic HPV16+ solid tumors

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Declaration of Interest

Jong Chul Park

Consulting and Advisory Role: ALB, Merck, I-Mab, Mito
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SQZ-PBMC-HPV-101: Underlying Technology and Mechanism

Prior cancer vaccines relied on cross-presentation, resulting in ineffective MHC-I presentation to CD8 T cells, limiting T cell activation and efficacy.

The Cell Squeeze® technology has demonstrated robust abilities to deliver antigens directly to the cytosol, thereby circumventing the cross-presentation process most vaccines rely on and enabling efficient MHC-I presentation and antigen-specific CD8 T cell activation.

Typical Cancer Vaccine Mechanism: Cross-Presentation

- Primary generates MHC-II presentation for CD4 and antibody responses
- Suited for prophylactic vaccines

Prioritizes creation of:
- CD4 helper cells
- Antibodies

SQZ™ APC Mechanism: Direct Presentation

- Primarily generates MHC-I presentation to CD8 T cells
- CD8 T cell responses in the tumor are highly correlated with patient outcomes

Prioritizes creation of:
- CD8 Killer T cells

SQZ™ vs. Cross Presentation Data

Hlavaty KA et al. AACR 2019 Abstract #3187.
Study Design and Cell Therapy Production

Inclusion Criteria
- Recurrent or metastatic
- HPV-driven cancer
- HPV-16+
- HLA-A *02+
- Platinum experienced
- CPI offered

Monotherapy Escalation
- SQZ-PBMC-HPV 5.0e6/kg Q3W Double Prime (n = 6)
- SQZ-PBMC-HPV 2.5e6/kg Q3W Double Prime (n = 4)
- SQZ-PBMC-HPV 2.5e6/kg Q3W (n = 5)
- SQZ-PBMC-HPV 0.5e6/kg Q3W (n = 3)

Combination De-escalation
- SQZ-PBMC-HPV RP2D + Atezolizumab 1200mg Q3W
- SQZ-PBMC-HPV RP2D + Ipilimumab 3mg/kg Q3W x 4
- SQZ-PBMC-HPV RP2D + Nivolumab 360mg Q3W
- SQZ-PBMC-HPV RP2D + Nivo 360mg Q3W + Ipi 1mg/kg Q6W

Treatment until PD, unacceptable toxicity or 2 years

Cell Therapy Production

Patient Leukapheresis
Day 1

SQZ Process <24-hours
Day 2

QC and Batch Release
Day 2-8

Administration to Patient
~1 week

The median time for manufacturing was 17 hours and allowed for a vein-to-vein time of about a week. Among all lots produced, the median viability was 91%.

In the highest dose cohort, a median of 5 doses were available for each patient.
### Patient Characteristics

- Heavily pretreated patient population with advanced disease at study entry.
- All but one patient (in the 2nd cohort) were treated with anti-PD-(L)1 checkpoint inhibitor, and the majority of them were considered refractory to a PD-1 inhibition.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median Age, years (min, max)</th>
<th>Female, n (%)</th>
<th>Caucasian Race, n (%)</th>
<th>Baseline ECOG PS of 1, n (%)</th>
<th>Phase 1 RMH Score High, n (%)</th>
<th>Site of primary tumor, n (%)</th>
<th>Metastatic Disease, n (%)</th>
<th>Median Number of Prior Lines, n (min, max)</th>
<th>Prior Systemic Therapy, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 M cells/kg SP (n=3)</td>
<td>65 (60, 68)</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>2 (67)</td>
<td>0 (0)</td>
<td>2 (66)</td>
<td>3 (100)</td>
<td>4 (2, 5)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>2.5 M cells/kg SP (n=5)</td>
<td>65 (54, 68)</td>
<td>3 (60)</td>
<td>5 (100)</td>
<td>3 (60)</td>
<td>3 (60)</td>
<td>3 (60)</td>
<td>5 (100)</td>
<td>3 (1, 7)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>2.5 M cells/kg DP (n=4)</td>
<td>49 (47, 66)</td>
<td>3 (75)</td>
<td>3 (75)</td>
<td>4 (100)</td>
<td>1 (100)</td>
<td>4 (100)</td>
<td>4 (100)</td>
<td>4 (3, 4)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>5.0 M cells/kg DP (n=6)</td>
<td>57.5 (52, 78)</td>
<td>0 (0)</td>
<td>5 (83)</td>
<td>3 (50)</td>
<td>1 (100)</td>
<td>1 (100)</td>
<td>6 (100)</td>
<td>3.5 (2, 6)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Total (n=18)</td>
<td>60 (47, 78)</td>
<td>9 (50)</td>
<td>16 (89)</td>
<td>12 (67)</td>
<td>8 (44)</td>
<td>7 (39)</td>
<td>2 (11)</td>
<td>4 (1, 7)</td>
<td>18 (100)</td>
</tr>
</tbody>
</table>

M=millions, SP=single-prime, DP=double-prime, ECOG PS=Eastern Cooperative Oncology Group Performance Status, ICI=immune checkpoint inhibitors, PD=Progressive Disease, BOR=Best Overall Response, RMH=Royal Marsden Hospital
**SQZ-PBMC-HPV Was Considered Safe and Well-Tolerated**

### Adverse Events

- Safety profile of SQZ-PBMC-HPV was consistent across all dose levels. Most related AEs were of low grade.
- One case of grade 2 cytokine release syndrome in a 1st cohort patient, which resolved in <24h, considered a related serious AE.
- Only grade ≥3 related adverse event was a case of grade 3 anemia in a 2nd cohort patient.
- No patients met the DLT criteria.

<table>
<thead>
<tr>
<th>Event</th>
<th>0.5 M cells/kg SP (n=3)</th>
<th>2.5 M cells/kg SP (n=5)</th>
<th>2.5 M cells/kg DP (n=4)</th>
<th>5.0 M cells/kg DP (n=6)</th>
<th>Total (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related AEs in &gt;1 Patient</td>
<td>3 (100)</td>
<td>4 (80)</td>
<td>2 (50)</td>
<td>5 (83)</td>
<td>14 (78)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>1 (20)</td>
<td>0</td>
<td>4 (67)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Flushing</td>
<td>1 (33)</td>
<td>0</td>
<td>0</td>
<td>2 (33)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (67)</td>
<td>1 (20)</td>
<td>0</td>
<td>0</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Infusion Related Reaction (IRR)</td>
<td>1 (33)</td>
<td>0</td>
<td>1 (25)</td>
<td>0</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (33)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>1 (20)</td>
<td>0</td>
<td>1 (17)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Related Grade ≥3 AEs</td>
<td>0</td>
<td>1 (20%)</td>
<td>0</td>
<td>0</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Related Serious AEs</td>
<td>1 (33%)(^2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>AEs of Special Interest(^3)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Dose-Limiting Toxicity</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Related AEs leading to d/c</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatal Related AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

1\(^1\) Grade 3 anemia. \(^2\) Grade 2 cytokine release syndrome (CRS). \(^3\) AEs of medical concern related to SQZ-PBMC-HPV mechanism of action (CRS, IRR). M=millions, SP=single-prime, DP=double-prime, AE=adverse events
Case Study: Patient 17

- 52-year-old man with squamous cell carcinoma of the oropharynx. Large primary lesion with significant symptoms burden.
- Initial diagnosis 3.7 years ago, with 6 prior lines of systemic therapy including carbo/5FU/pembro and anti-TGFβ/pembro (BOR=PD) 9 months before SQZ-PBMC-HPV dosing.
- Received all 7 doses of SQZ-PBMC-HPV, with excellent tolerability (G1 flushing, G1 fatigue).
- Marked symptomatic improvement (dysphagia and neck swelling) and improvement of the lesion on physical examination.

Day-28 on treatment biopsy demonstrated an 8-fold increase in tumor infiltrating CD8 cells.

Radiographic response, including confirmed CR on target lesion (mediastinal lymph node (RECIST 1.1) with a new dermal lesion at the last tumor assessment.

Highest dose cohort changes in CD8 TILs

**Highest dose cohort tumor measurements**

(n = 5 patients)
SQZ-PBMC-HPV Turns TME into Inflamed Phenotype in Responding Patient

**Case Study: Patient 17**

- Massive influx of CD8 cells into the tumor changed immunophenotype from desert to inflamed.
- Increase in HLA-I expression likely due to CD8 driven IFN-γ secretion.
- Significant reduction in frequency of E6 expressing cells as measured by RNA-ISH. E7 expressing cells follow the same pattern (not shown).
- Increase in PD-L1 expression suggests potential synergy with a combinatory approach.
Conclusions and Future Development for SQZ-PBMC-HPV

**Conclusion**

- **Safety:** SQZ-PBMC-HPV was considered safe and well-tolerated at all dose levels. Safety profile consisted of mostly low grade (grades 1 and 2) non-specific AEs, only one related serious adverse event, and no dose-limiting toxicities observed.

- **Manufacturability:** All batches produced under cGMP yielding multiple cryopreserved doses in <24hrs with ~1wk vein-to-vein. Product characterization confirmed antigen presentation and high viability in all patient batches.

- **Clinical Activity:** Radiographic and pathological correlation in patients deriving clinical benefit. Patient 17's clinical response consistent with expected SQZ APC mechanism: increased CD8 tumor infiltration, reduction of E6 and E7 expressing cells suggests antigen-specific killing, increased PD-L1 expression consistent with tumor inflammation.

**Future Development**

- SQZ-PBMC-HPV at 5.0M cells/kg dose was endorsed by study DSMB to move into PD-(L)1 & CTLA-4 combination cohorts.
- The highest dose cohort is still enrolling to further characterize efficacy of SQZ-PBMC-HPV as monotherapy.
We thank the patients and their families!

Additional information may be found at: