Phase 1 dose escalation of IMC-F106C, the first PRAME × CD3 ImmTAC bispecific protein in solid tumors

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DECLARATION OF INTERESTS

Dr Omid Hamid

Advisory/Consulting: Aduro Biotech, Akeso Biopharma, Alkermes, Amgen, BeiGene, BioAtla, BMS, Genentech, GlaxoSmithKline, Idera, Immunocore, Incyte, Iovance Biotherapeutics, Janssen, Merck, NextCure, Novartis, Pfizer, Regeneron, Roche, Sanofi, Seattle Genetics, Tempus, Zelluna; Speaker’s Bureau: BMS, Novartis, Pfizer, Sanofi/Regeneron

Honoraria: BMS, Novartis, Pfizer, Sanofi/Regeneron

Research Funding (Institute): Aduro Biotech, Akeso Biopharma, Amgen, Arcus Biosciences, Bioatla, BMS, CytomX Therapeutics, Exelixis, Genentech, GlaxoSmithKline, Idera, Immunocore, Incyte, Iovance Biotherapeutics, Merck, Merck Serono, Moderna Therapeutics, NextCure, Novartis, Pfizer, Regeneron, Roche, Rubius Therapeutics, Sanofi, Seattle Genetics, Torque, Zelluna

DISCLAIMER

All statements contained in this presentation are based on preclinical and clinical trial data related to an investigational molecule, IMC-F106C. Development of this molecule is ongoing and, therefore, statements relating to study data to date should not be regarded as definitive reflections of safety, efficacy or the risk-benefit profile of the molecule.
IMC-F106C: ImmTAC targeting HLA-A2-presented peptide from PRAME (PRAME × CD3)

**PRAME**: most broadly expressed cancer-testis antigen in several tumor types but with minimal normal tissue expression

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Prevalence of PRAME expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma, endometrial, NSCLC, TNBC, SCLC, ovarian</td>
<td>HIGH</td>
</tr>
<tr>
<td>RCC, esophageal, SCCHN, cervical</td>
<td>LOW</td>
</tr>
<tr>
<td>Bladder, HCC, gastric</td>
<td>LOW</td>
</tr>
</tbody>
</table>
Phase 1 Study Design

**Key objectives**

### Primary endpoint
- Determine MTD/expansion dose

### Secondary endpoints
- Preliminary antitumor activity
- Pharmacokinetics
- Pharmacodynamic markers

**Key eligibility criteria**
- HLA-A*02:01 (central testing)
- Select advanced solid tumors
- Tumor PRAME by immunohistochemistry
  - High PRAME prevalence: enroll all comers; test retrospectively
  - All other indications: prospective confirmation of PRAME

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**Screening**

Weekly IV infusion with intra-patient dose escalation (over 3 weeks)

**Treatment**

Tumor assessment every 9 weeks

**Follow-up**

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**Dose escalation**

**Target Dose, Starting Day 15**

- 320 mcg
- 160 mcg
- 80 mcg
- 40 mcg
- 20 mcg
- 0.3 - 10 mcg

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**Total safety population N=55**

**Efficacy population n=31**

* Of 36 patients treated at target escalation dose of ≥20 mcg, 5 patients were excluded from efficacy analyses as they were PRAME-negative (n=2) or not yet had tumor assessment (n=3)

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EudraCT No. 2019-004046-16; NCT04262466

Data cut-off date: 18 Jul 2022

IV, intravenous; MTD, maximum tolerated dose

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PARIS 2022: ESMD Congress

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* Of 36 patients treated at target escalation dose of ≥20 mcg, 5 patients were excluded from efficacy analyses as they were PRAME-negative (n=2) or not yet had tumor assessment (n=3)
Strong and Consistent Pharmacodynamic Activity at ≥20 mcg IMC-F106C
T cell activation and re-direction into tumor seen across ImmTAC platform

Interferon induction

T cell trafficking

Peripheral blood

Peripheral blood

Results plotted as mean ± SEM
Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Safety Population N=55</th>
<th>Efficacy Population N=31†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — median yr (range)</td>
<td>60 (26, 79)</td>
<td>61 (36, 79)</td>
</tr>
<tr>
<td>ECOG status 0 — n (%)</td>
<td>30 (55%)</td>
<td>19 (61%)</td>
</tr>
<tr>
<td><strong>PRAME status (IHC)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>49 (89%)</td>
<td>28 (90%)</td>
</tr>
<tr>
<td>Negative</td>
<td>2 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>4 (7%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Median H-score</td>
<td>195</td>
<td>188</td>
</tr>
<tr>
<td><strong>Tumor type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>34 (62%)</td>
<td>17 (55%)</td>
</tr>
<tr>
<td>Uveal (UM)</td>
<td>26 (47%)</td>
<td>11 (35%)</td>
</tr>
<tr>
<td>Cutaneous (CM)*</td>
<td>8 (15%)</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>Ovarian Carcinoma</td>
<td>10 (18%)</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Serous (SOC)*</td>
<td>7 (13%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Non-serous</td>
<td>3 (5%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>4 (7%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>TNBC*</td>
<td>3 (5%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Endometrial*</td>
<td>4 (7%)</td>
<td>2 (6%)</td>
</tr>
</tbody>
</table>

- Median PRAME H-score in efficacy population was high, 188; most patients enrolled regardless of PRAME testing
- Patients in efficacy population were heavily pretreated
  - Ovarian: all platinum resistant
  - CM: all received prior anti-PD1 and anti-CTLA4
  - NSCLC: all received prior anti-PD1
  - TNBC and endometrial: 2-5 prior lines of therapy

* In efficacy population, these tumors enrolled regardless of PRAME immunohistochemistry (IHC) testing, which was evaluated retrospectively. NSCLC squamous also enrolled regardless of PRAME testing
† Of 36 patients treated at target escalation dose of ≥20 mcg, 5 patients were excluded from efficacy analyses as they were PRAME-negative (n=2) or not yet had tumor assessment (n=3)
**IMC-F106C was well tolerated**
Most frequent related AE was Grade 1/2 CRS, consistent with proposed mechanism

<table>
<thead>
<tr>
<th>Preferred Term (MedDRA v23.1)</th>
<th>0.3 – 10 mcg† (N=18)</th>
<th>20 – 320 mcg† (N=37)</th>
<th>Total (N=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Grades (events in ≥ 25% of patients), n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AT LEAST ONE EVENT</td>
<td>18 (100)</td>
<td>34 (92)</td>
<td>52 (95)</td>
</tr>
<tr>
<td>Pyrexia*</td>
<td>10 (56)</td>
<td>21 (57)</td>
<td>31 (56)</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>5 (28)</td>
<td>22 (59)</td>
<td>27 (49)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (33)</td>
<td>13 (35)</td>
<td>19 (35)</td>
</tr>
<tr>
<td>Hypotension*</td>
<td>3 (17)</td>
<td>15 (41)</td>
<td>18 (33)</td>
</tr>
<tr>
<td>Chills</td>
<td>9 (50)</td>
<td>8 (22)</td>
<td>17 (31)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (39)</td>
<td>10 (27)</td>
<td>17 (31)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (17)</td>
<td>12 (32)</td>
<td>15 (27)</td>
</tr>
<tr>
<td><strong>Grade ≥ 3 (Events in &gt; 1 patient), n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AT LEAST ONE EVENT</td>
<td>6 (33)</td>
<td>13 (35)</td>
<td>19 (35)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>1 (6)</td>
<td>7 (19)</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>3 (17)</td>
<td>1 (3)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (6)</td>
<td>2 (5)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>2 (11)</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (6)</td>
<td>1 (3)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Pyrexia*</td>
<td>0</td>
<td>2 (5)</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

- MTD not reached
- No treatment-related discontinuation or Grade 5 adverse events
- CRS events were all manageable
  - Majority (77%) within first 3 doses
  - 71% Grade 1
  - 29% Grade 2
  - No Grade ≥ 3 CRS
- Adverse events attenuate over time

* Includes events reported as a sign/symptom of CRS
† Safety presented by intended target escalation dose on Day 15. 1/37 patients received only a single dose of 2 mcg and did not reach target dose of ≥ 20 mcg
Responses observed in multiple tumor types

- Two patients (1 with NSCLC, 1 serous ovarian) discontinued treatment due to PD with scan data not available at DCO
- Ovarian cancer patient with unconfirmed PR (uPR) remains on treatment and eligible for confirmation
- PRAME expression assessed by IHC H-score
- Two PRAME-negative patients both had PD (not shown)

Endo, endometrial carcinoma; NSCLC, non small cell lung carcinoma; TNBC, triple-negative breast cancer;
Majority of patients have durable tumor response or disease stabilization.
Responses are durable, 6 of 7 PRs still ongoing

Two PRs ongoing for 7+ months

<table>
<thead>
<tr>
<th>Indication</th>
<th>Best ctDNA change</th>
<th>PRAME expression*</th>
</tr>
</thead>
<tbody>
<tr>
<td>UM Naive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutaneous melanoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serous Ovarian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UM Prior Tebentafusp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian carcinosarcoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* PRAME expression assessed by IHC H-score

Endo, endometrial carcinoma; NSCLC, non small cell lung carcinoma; TNBC, triple-negative breast cancer; UM, uveal melanoma; ctDNA, circulating tumor DNA; ND, not yet determined (9 patients pending); NE, not evaluable; PR, partial response
Reduction in circulating tumor DNA observed across tumor types (n=20)†

- 4 PR patients evaluated for ctDNA had > 50% reduction, including 3 with clearance
- Two patients had ctDNA clearance despite best response of PD

† 20 of 31 efficacy evaluable patients had paired ctDNA. Data not yet available for 9 patients, including 3 PRs. Two patients did not have baseline detectable ctDNA.

B, triple-negative breast cancer; C, cutaneous melanoma; ctDNA, circulating tumor DNA; E, endometrial carcinoma; LA, non small cell lung adenocarcinoma; LS, non small cell lung squamous cell carcinoma; O, ovarian; U, uveal melanoma; CPI, checkpoint inhibitor; tebe, tebentafusp
Example responders: ovarian carcinoma and uveal melanoma

Patient #1
Ovarian cancer
5 prior lines, platinum resistant

Baseline

On treatment

Unconfirmed PR
Ongoing treatment; ctDNA pending

Week 9

Patient #2
Uveal Melanoma

Baseline

Representative lesion

On treatment

Confirmed PR
tDNA cleared
Ongoing treatment 1+ year

Week 18

Images courtesy of Dr. Marlama Orloff (TJU) and Dr. Anja Williams (SCRI-UK)
Example responder: cutaneous melanoma
Prior anti-CTLA4, multiple anti-PD1s and oncolytic virus

Patient #3
Baseline

Confirmed PR
ongoing treatment 5+ months

Images courtesy of Dr. Omid Hamid (Angeles Clinic)
Example responder: serous ovarian carcinoma
5 prior regimens including platinum, bevacizumab, anti-PD-1, investigational agents

Patient #4
Baseline

Confirmed PR
ctDNA 67% decrease
nontarget PD at Month 8 but ongoing treatment 1+ yr

Images courtesy of Dr. Omid Hamid (Angeles Clinic)
Conclusions

- IMC-F106C, first PRAME×CD3 ImmTAC, activates T cells and is well-tolerated
  - CRS is mostly Grade 1, no Grade ≥3, and predominantly during initial 3 doses
  - Treatment-related AEs are manageable; none have led to discontinuation or death

- Durable (up to 9+ months) RECIST PRs across multiple tumor types, including
  - Cutaneous melanoma, progressed following prior anti-PD1 and anti-CTLA4
  - Heavily pre-treated, platinum-resistant ovarian carcinoma
  - Uveal melanoma

- Benefit also apparent in disease control, including conversion of SD to PR

- Almost all evaluable patients, across multiple tumor types, have ctDNA reduction
  - Early reduction appears associated with clinical benefit
  - Complete ctDNA clearance common in melanoma

- Expansions open in cutaneous melanoma, NSCLC, endometrial and ovarian carcinoma

- Dose escalation continues and combinations with chemotherapy and checkpoint inhibitors planned
Thank you to all patients, their families and their caregivers who were involved in this global clinical trial & all investigators and their teams

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