Lemzoparlimab: A Differentiated CD47 Mab in Clinical Study

Drug safety, PK profile and preliminary clinical efficacy in solid tumors

Presented at 2020 SITC
SAFE HARBOUR STATEMENT

This presentation is on a drug candidate in clinical development and includes information from studies and information that might be considered forward-looking. While these forward-looking statements represent our current judgment based on current information, please be aware they are subject to risks and uncertainties as development progresses that could cause actual results to differ materially. I-Mab Biopharma does not undertake any obligation to update or revise forward looking statements in this presentation.

CONFIDENTIALITY

This presentation and the information in it are confidential and are provided for the sole purpose of exploring business opportunities between I-Mab Biopharma and you for the project TJC4. The slide deck and information related to TJC4 may not be disclosed to any third party or used for any other purpose without the consent of I-Mab Biopharma.
Lemzoparlimab
A single agent dose escalation study in patients with solid tumor
1mg/kg, 3mg/kg, 10mg/kg, 20mg/kg, 30mg/kg, Q1W

Drug safety  PK profile  Receptor occupancy
Patient demographics of Phase I trial in US

- Twenty patients with advanced and heavily treated solid tumors were enrolled
Well tolerated with no DLT and no severe or hemolytic anemia

- Lemzoparlimab appears safe and well-tolerated up to 30 mg/kg on a weekly basis **without priming dosing strategy**.

- **No dose-limiting toxicity** was observed and MTD was not reached.

- The most frequent adverse events included fatigue and transient and low-grade anemia. No clinical or laboratory evidence of hemolytic anemia were observed throughout.

- TRAEs include low-grade anemia (**Grade 1 or Grade 2**) and one case of Grade 3 lipase increase.

## AE TERMS

<table>
<thead>
<tr>
<th>AE TERM</th>
<th>1mg/kg (N=4)</th>
<th>3mg/kg (N=4)</th>
<th>10mg/kg (N=4)</th>
<th>20mg/kg (N=5)</th>
<th>30mg/kg (N=3)</th>
<th>Total (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gr Any</td>
<td>Gr Any</td>
<td>Gr Any</td>
<td>Gr Any</td>
<td>Gr Any</td>
<td>Gr Any</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Blood LDH decreased</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Chills</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Copyright © 2020 I-MAB BIOPHARMA, All Rights Reserved
A transient reduction in the hemoglobin levels during the first cycle was observed across all cohorts. The average drop was ~10% and was not dose dependent.

This finding is consistent with the results of pre-clinical GLP toxicity studies.
The PK profile of lemzoparlimab appeared linear at the doses higher than 10 mg/kg following a single dose, while its exposure was greater than dose proportional over the dose range of 1 to 10 mg/kg, suggesting that at higher doses, lemzoparlimab can overcome the CD47 sink effect.

Five subjects were confirmed positive for anti-drug antibodies (ADA) following the first treatment: 3 were from 1 mg/kg, 1 from 3 mg/kg and 1 from 10 mg/kg. No impact of ADA was seen on safety or PK.
Maximal receptor occupancy at 20mg/kg and 30mg/kg

- A dose dependent increase of the CD47 receptor occupancy (RO) on CD3+ T cells in the peripheral blood was observed after the escalation of the lemzoparlimab dosage.
- Maximal saturation of CD47 on peripheral T cells was achieved at 20 and 30 mg/kg following weekly administration of lemzoparlimab.
Lemzoparlimab
A single agent dose escalation study in patients with solid tumor
1mg/kg, 3mg/kg, 10mg/kg, 20mg/kg, 30mg/kg, Q1W

Preliminary monotherapy clinical anti-tumor activity
Preliminary efficacy assessment (cutoff Nov 10, 2020)

- **One confirmed PR** in 30mg/kg cohort (n=3).
- **Three patients achieved SD** (stable disease).

  * One showed reduction of 25% at first scan (10mg/kg).
  ** One with SD (15% reduction) continued on therapy (30mg/kg)
Preliminary efficacy: One Confirmed PR at 30mg/kg (n=3)

74 years old male with metastatic melanoma (liver metastases)

- **Prior therapy**: Progressed on 6-month treatment with nivolumab alone and ipilimumab/nivolumab combination therapy (PD-L1 level not available)
- **Initial partial response (PR)** on cycle 3 day 1 (C3D1) on Aug 3, 2020 (↓ 33%)
- **Confirmed PR** (↓ 31.45%)
- **Ongoing PR** (↓ 34.73%) on treatment
Preliminary efficacy with individual treatment durations

- The longest treatment duration 280 days
- PR: time to response: 2 months
- Patients in 30mg/kg cohort continued
Lemzoparlimab Data Summary

Good drug safety without priming dosing
- All TRAEs were mild
- A non-dose dependent transient reduction (~10%) in the hemoglobin levels was observed during the first treatment cycle.

Favorable PK profile with no significant “sink effect” at higher doses

Promising efficacy signal with monotherapy
- 1 confirmed PR (metastatic melanoma) together with 3 SD in 16 evaluable patients

Maximal CD47 receptor occupancy at 20 mg/kg and 30 mg/kg

References: Other Ph 1 studies with CD47 antibody as single agent treatment in patients with solid tumor

Letalplimab (Innovent, Lakhani et al, poster #625, SITC 2020)
- Priming dosing required
- Three patients had Grade 3 TRAEs (Grade 3 blood bilirubin increase, Grade 4 platelet count decrease and Grade 3 anemia, each in 1 patient). Three of 20 patients (15%) had anemia, an expected TRAE associated with the mechanism of IBI188
- Quote by the company: “Letaplismab monotherapy does not show single agent activity in solid tumor”

Magrolimab (Forty-Seven, Branimir IS, etc. JCO 2019)
- Two PRs observed out of 29 patients (20 mg/kg) with advanced solid tumors while no efficacy was seen at 30 mg/kg (n=9) and 45 mg/kg (n=6).
- Grade 3 anemia in 17% treated patients.
Lemzoparlimab – A Differentiated CD47 Antibody in Clinical Development

Previously presented at 2019 ASH and 2020 CD47 summit
**Disclaimer**

**SAFE HARBOUR STATEMENT**

This presentation is on a drug candidate in clinical development and includes information from studies and information that might be considered forward-looking. While these forward-looking statements represent our current judgment based on current information, please be aware they are subject to risks and uncertainties as development progresses that could cause actual results to differ materially. I-Mab Biopharma does not undertake any obligation to update or revise forward looking statements in this presentation.

**CONFIDENTIALITY**

This presentation and the information in it are confidential and are provided for the sole purpose of exploring business opportunities between I-Mab Biopharma and you for the project TJC4. The slide deck and information related to TJC4 may not be disclosed to any third party or used for any other purpose without the consent of I-Mab Biopharma.
Hematologic toxicity
A major challenge for CD47 antibody as a cancer therapy
CD47 is a “marker of self” on red blood cells (RBC)

**Part of the Rh complex**
- RhCE/D antigens
- Rh-associated glycoprotein (RhAG)
- CD47

**High levels of CD47 on RBCs**

**CD47 as a switch for erythrocyte phagocytosis**

*Transfusion 2019;59:730-737*

*ISBT Science Series 8.1:153-156*

**CD47 as a molecular switch turn on/off phagocytosis**
Most of CD47 antibodies, including the most advanced CD47 mAb 5F9, demonstrated a significant binding affinity to normal RBCs.

Grade 3 hemagglutination (DLT) was observed at 3mg/kg without priming and 1, 20 mg/kg with priming of 5F9.
Generation of a differentiated CD47 antibody (TJC4 or lemozoparlimab) by design
Screen for a differentiated CD47 mAb by design

**Our “Point-of-Differentiation”**

**For** strong binding to tumor cells

**Against** binding to RBC

- **Using phage library** to identify CD47 Abs with rare epitopes
- **Introducing RBCs as counter-screen** for minimal binding

- **Panning of CD47 binders using phage library**
- **Screening of functional CD47 lead Abs**
- **Screening for RBC-sparing properties**
- **CMC and pre-clinical dev.**
- **Final candidate molecule lemzoparlimab**
Strong anti-tumor activity by lemzoparlimab

*In vitro* binding potency and phagocytosis of tumor cells

- A panel of 12 tumor cell lines across different tumor lineages including both leukemic and solid tumor lineages was used to evaluate the binding and phagocytosis of lemzoparlimab (TJC4) and 5F9 (in-house produced based upon the published sequence).
- Lemzoparlimab (TJC4) showed a comparable pattern of binding intensity with 5F9 on the 12 cell lines tested, which was closely correlated with the phagocytosis pattern of lemzoparlimab (TJC4) and 5F9 in the same tumor cell lines.
Primary CD33+ tumor blasts from different AML patients were used to evaluate the binding, SIRPa blocking and phagocytosis of lemzoparlimab (TJC4) and 5F9.

Lemzoparlimab (TJC4) showed a comparable potency in the binding, SIRPa blocking and phagocytosis of primary AML tumor cells with 5F9 across different concentrations.
Inject $1 \times 10^6$ Luci-Raji cells via tail vein in NSG mice

CD47 Abs treatment started 5 days post engraftment

*i.p.* injection q2d

- Treatment of lemzoparlimab (TJC4) eradicated the engrafted tumor cells, which was comparable to 5F9 and 2A1 reference anti-CD47 antibodies.
NSG mice transplanted intravenously with HL-60 cells were treated with lemzoparlimab (TJC4) once every five days (n=10/group). The survival rate of the treated mice was analyzed.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>MST (days)</th>
<th>ILS (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vehicle control</td>
<td>39 (a) (33~49)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>TJC4 (0.4 mg/kg)</td>
<td>&gt;63 (63~&gt;63)</td>
<td>&gt;61.5</td>
<td>(b&lt;0.0001)</td>
</tr>
<tr>
<td>3</td>
<td>TJC4 (2 mg/kg)</td>
<td>&gt;61 (49~&gt;63)</td>
<td>&gt;57.1</td>
<td>(b&lt;0.0001)</td>
</tr>
<tr>
<td>4</td>
<td>TJC4 (10 mg/kg)</td>
<td>&gt;63</td>
<td>&gt;61.5</td>
<td>(b&lt;0.0001)</td>
</tr>
</tbody>
</table>

MST: Median survival time; ILS: in life-span
\(a\): The range of survival times

Strong anti-tumor activity by lemzoparlimab

*In vivo* anti-tumor activity (HL-60 leukemia model)
**Strong anti-tumor activity by lemezoparlimab**

*In vivo* anti-tumor activity in combination with Rituximab (DLBCL model)

Inject WSU-DLCL2 cell line s.c into NOD/SCID mice

Start the antibody treatment *i.p* biw

Tumor volume reached ~100 mm³

Tumor growth

Body weight change

---

**NOD/SCID mice were subcutaneously injected with WSU-DLCL2 human diffuse large B cell lymphoma cells and treated with lemezoparlimab (TJC4) as a single agent and in combination with rituximab twice a week.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Tumor Size (mm³) on day 43</th>
<th>TGI (%)</th>
<th>T/C (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vehicle</td>
<td>2161.32±252.88</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Rituximab 5mg/kg</td>
<td>1578.37±241.53</td>
<td>27</td>
<td>73</td>
<td>0.376</td>
</tr>
<tr>
<td>3</td>
<td>TJC4 5mg/kg</td>
<td>2148.89±227.87</td>
<td>1</td>
<td>99</td>
<td>1.000</td>
</tr>
<tr>
<td>4</td>
<td>Rituximab+ TJC4 5mg/kg+5mg/kg</td>
<td>794.9±174.05</td>
<td>63</td>
<td>37</td>
<td>0.004</td>
</tr>
</tbody>
</table>

TGI: Tumor growth inhibition; T/C: Treat/Vehicle control

Statistics: One-way ANOVA analysis for tumor volume

---
Differentiated property of lemzoparlimab
Human RBC binding and agglutination

- Lemzoparlimab did not induce RBC agglutination and exerted minimal RBC binding as compared to 5F9 and 2A1.
Differentiated property of lemozoparlimab
Effects on RBC and hemoglobin levels in cynomolgus monkeys

### Pilot-single dose

<table>
<thead>
<tr>
<th></th>
<th>RBCs</th>
<th>Hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBS</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td>5F9</td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
<tr>
<td>TJC4</td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
</tbody>
</table>

### Pilot-repeat dose

<table>
<thead>
<tr>
<th></th>
<th>RBCs</th>
<th>Hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBS</td>
<td><img src="image7" alt="Graph" /></td>
<td><img src="image8" alt="Graph" /></td>
</tr>
<tr>
<td>TJC4</td>
<td><img src="image9" alt="Graph" /></td>
<td><img src="image10" alt="Graph" /></td>
</tr>
</tbody>
</table>

### 4-wk GLP-Tox

#### Male

<table>
<thead>
<tr>
<th></th>
<th>RBCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td><img src="image11" alt="Graph" /></td>
</tr>
<tr>
<td>TJC4 (10 mg/kg)</td>
<td><img src="image12" alt="Graph" /></td>
</tr>
<tr>
<td>TJC4 (30 mg/kg)</td>
<td><img src="image13" alt="Graph" /></td>
</tr>
<tr>
<td>TJC4 (100 mg/kg)</td>
<td><img src="image14" alt="Graph" /></td>
</tr>
</tbody>
</table>

#### Female

<table>
<thead>
<tr>
<th></th>
<th>RBCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td><img src="image15" alt="Graph" /></td>
</tr>
<tr>
<td>TJC4 (10 mg/kg)</td>
<td><img src="image16" alt="Graph" /></td>
</tr>
<tr>
<td>TJC4 (30 mg/kg)</td>
<td><img src="image17" alt="Graph" /></td>
</tr>
<tr>
<td>TJC4 (100 mg/kg)</td>
<td><img src="image18" alt="Graph" /></td>
</tr>
</tbody>
</table>
Underlying mechanism of lemzoparlimab
Unique epitope revealed by crystal structure of TJC4/CD47 complex

<table>
<thead>
<tr>
<th>Crystal structure of mAb/CD47 complex</th>
<th>TJC4</th>
<th>5F9</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD47 mAb</td>
<td>CD47 mAb</td>
<td>The crystal structure of TJC4/CD47 complex adopts straighter head to head orientation, unlike the structure of 5F9/CD47 complex presenting tilted head to head orientation.</td>
<td></td>
</tr>
<tr>
<td>Human CD47</td>
<td>Human CD47</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Further analysis of the crystal structure demonstrated that lemzoparlimab (TJC4) binds to a different epitope of CD47 protein as compared to 5F9, which suggests that this unique binding epitope may be related with the minimal RBC binding property of lemzoparlimab (TJC4)
Hypothesis: Potential glycosylation of CD47 on RBCs may prevent the binding of lemzoparlimab (TJC4)

- CD47 as a glycoprotein is heavily glycosylated. There are six potential N-glycosylation sites, five of which are in extra-cellular IgV domain
- Crystal structure analysis identified a predicted N glycosylation site which is located near the epitope residues. It may influence the epitope exposure and affect the binding of lemzoparlimab (TJC4)

Results: De-glycosylation of RBCs restored the binding of lemzoparlimab (TJC4)

- PNGase treatment of RBCs to remove the N-linked oligosaccharides from glycoproteins significantly increased the binding of lemzoparlimab (TJC4), while not affecting the binding of 5F9
Executive summary of lezmoparlimab

- Minimal binding to RBCs without significant anemia seen in non-human primates even at a high dose (100 mg/kg)
- Strong anti-tumor efficacy in different tumor models

- Unique glyco-epitope and underlying MoA identified with differentiated properties

- A stable cell line with a good titer
- Robust process developed and 2 batches of 1,000L GMP production completed

- Safety differentiation in solid tumor
- Favorable PK profile with a less sink effect
- No need for a priming dosing regimen
- I-Mab and AbbVie will collaborate to jointly develop lezmoparlimab for multiple cancer indications

Minimal binding to RBCs without significant anemia seen in non-human primates even at a high dose (100 mg/kg)

Strong anti-tumor efficacy in different tumor models

Unique glyco-epitope and underlying MoA identified with differentiated properties

A stable cell line with a good titer
Robust process developed and 2 batches of 1,000L GMP production completed

Safety differentiation in solid tumor
Favorable PK profile with a less sink effect
No need for a priming dosing regimen
I-Mab and AbbVie will collaborate to jointly develop lezmoparlimab for multiple cancer indications
Thank You!

I-Mab Business Contact:
Weimin Tang, EVP of BD
weimin.tang@i-mabbiopharma.com
Zhen Pang, Senior Director of BD
zhen.pang@i-mabbiopharma.com

I-Mab Investor Contact:
Jielun Zhu
Chief Financial Officer
(86) 21 6057 5788
jielun.zhu@i-mabbiopharma.com