CD47 Directed Therapy in B-Cell Malignancies

Workshop on Tumor Immune Interactions in Lymphoid Malignancies

Presented by Bob Uger at the 2018 ASH Annual Meeting
Macrophages and Antitumor Responses

- Macrophages are phagocytes that engulf and digest cells, debris, etc.
- They are found in abundance in the tumor microenvironment
- Often thought of as “bad actors”, promoting tumor growth and immune suppression
- But..
  - Macrophages are known to mediate effects of targeted cancer antibodies (ADCP)
  - The antitumor effect of macrophages is frequently suppressed by CD47, an innate immune checkpoint
CD47 – An Innate Checkpoint that Inhibits Macrophage Phagocytosis

- CD47 is a widely expressed glycoprotein that delivers a “DO NOT EAT” signal to macrophages through SIRPα.
- Binding of CD47 to SIRPα inhibits macrophage cytoskeletal activity.
- The regulation of phagocytosis by the CD47-SIRPα axis was first discovered in the context of erythrocyte clearance.
- Tumor cells frequently exploit the CD47-SIRPα axis to evade immune surveillance by macrophages.
CD47 as a Target in B-Cell Malignancies

CD47 is frequently overexpressed on malignant B-cells

High CD47 expression correlates with poor survival

Chao et al. 2010 Cell
Blockade of CD47 Has Anti-Tumor Activity in Preclinical Studies

**In Vitro Phagocytosis by Macrophages**

+ Control Fc
No CD47 blockade

+ TTI-621 (SIRPαFc)
CD47 blockade

**DLBCL Xenograft model**

Lin et al. 2017 PLoS One
The Fc Region Impacts the Potency of CD47 Blocking Agents

- Preclinical studies demonstrate a potency hierarchy: IgG1 > IgG4 > inert IgG
- Maximum potency requires CD47 blockade plus a strong “eat” signal:
  - IgG1 Fc built into the blocking agent, OR
  - Second IgG1 antibody binding the tumor cells (e.g., rituximab)
- IgG1-based blockers are more likely to have monotherapy activity; IgG4- and inert Fc- agents are better suited for combinations
### CD47 Directed Agents in Clinical Development for B-Cell Malignancies

<table>
<thead>
<tr>
<th>Agent (Company)</th>
<th>Format</th>
<th>Isotype</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu5F9 (Forty Seven)</td>
<td>Antibody</td>
<td>IgG4</td>
<td>Phase II (NCT02953509)</td>
</tr>
<tr>
<td>CC-9002 (Celgene)</td>
<td>Antibody</td>
<td>IgG4</td>
<td>Phase I (NCT02367196)</td>
</tr>
<tr>
<td>SRF231 (Surface Oncology)</td>
<td>Antibody</td>
<td>IgG4</td>
<td>Phase I (NCT03512340)</td>
</tr>
<tr>
<td>IBI188 (Innovent Biologics)</td>
<td>Antibody</td>
<td>IgG4</td>
<td>Phase I (NCT03717103)</td>
</tr>
<tr>
<td>TTI-621 (Trillium Therapeutics)</td>
<td>Decoy Receptor</td>
<td>IgG1</td>
<td>Phase I (NCT02663518)</td>
</tr>
<tr>
<td>TTI-622 (Trillium Therapeutics)</td>
<td>Decoy Receptor</td>
<td>IgG4</td>
<td>Phase I (NCT03530683)</td>
</tr>
<tr>
<td>ALX148 (ALX Oncology)</td>
<td>Decoy Receptor</td>
<td>Inert IgG1</td>
<td>Phase I (NCT03013218)</td>
</tr>
</tbody>
</table>

Clinical Data reported
5F9 (Forty Seven Inc.) is a humanized IgG4, CD47-blocking antibody.

Rituximab combination data reported for 22 pts (15 DLBCL, 7 FL).

Pts received a 1 mg/kg priming dose followed by 10, 20 or 30 mg/kg 5F9 weekly; all cohorts received standard dose rituximab.

Dosing achieved 100% target saturation in periphery.

Most common AEs: Anemia (41%), headache (41%), infusion-related reactions (38%).

Anemia mitigated by priming dose that triggers compensatory reticulocytosis.

Advani et al. 2018 NEJM

More information on the mechanism of anemia resistance to be presented at the Sunday poster session (Abstract 2327).
5F9 + Rituximab Shows Promising Activity in Patients with Aggressive and Indolent B-cell NHL

Table 2. Clinical Responses to Combination Therapy with 5F9 and Rituximab.\(^a\)

<table>
<thead>
<tr>
<th>Response</th>
<th>All Patients (N = 22)</th>
<th>Patients with DLBCL (N = 15)</th>
<th>Patients with Follicular Lymphoma (N = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>11 (50)</td>
<td>6 (40)</td>
<td>5 (71)</td>
</tr>
<tr>
<td>Complete response</td>
<td>8 (36)</td>
<td>5 (33)</td>
<td>3 (43)</td>
</tr>
<tr>
<td>Partial response</td>
<td>3 (14)</td>
<td>1 (7)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3 (14)</td>
<td>3 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>8 (36)</td>
<td>6 (40)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Disease control</td>
<td>14 (64)</td>
<td>9 (60)</td>
<td>5 (71)</td>
</tr>
</tbody>
</table>

\(^a\) Objective response was defined as a complete or partial response. Disease control was defined as a complete response, partial response, or stable disease.

A Change in Tumor-Lesion Burden among Patients with DLBCL

B Change in Tumor-Lesion Burden among Patients with DLBCL

C Change in Tumor-Lesion Burden among Patients with Follicular Lymphoma

Advani et al. 2018 NEJM
TTI-621: An IgG1 SIRPαFc Decoy Receptor

• TTI-621 (Trillium) is a dual function CD47 blocking decoy receptor
• Does not bind to human RBCs
• In a phase I study in R/R hematologic malignancies (weekly IV infusion)
• Safety data reported for 163 pts; most frequent AEs were low grade infusion reactions
• ≥ G3 thrombocytopenia occurred in 19% of patients
• A conservative DLT definition led to an MTD of 0.2 mg/kg; dose intensification currently in progress
TTI-621 Thrombocytopenia is Transient and Not Associated with Increased Risk of Bleeding

- Thrombocytopenia is likely an on-target effect resulting from CD47 blockade and the TTI-621 IgG1 Fc
- Thrombocytopenia is reversible within a week
- Pre-dose platelet levels remain relatively stable over the course of the study
- Transient platelet decreases did not lead to an increased risk of bleeding
- Platelet decreases did not impact drug delivery – 1/163 patients had dosing discontinued due to thrombocytopenia
Low Dose TTI-621 Has Activity as Monotherapy and in Combination with Rituximab in DLBCL Patients

- DLBCL efficacy:
  - 25% ORR monotherapy
  - 25% ORR rituximab combo

- Majority of responses were observed in patients receiving weekly doses of 0.2 mg/kg (monotherapy, 2/2 pts) or 0.1 mg/kg (combination, 8/9 pts)

### TTI-621 Monotherapy

<table>
<thead>
<tr>
<th>N</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>ORR Time to Resp</th>
<th>Tmt Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>8</td>
<td>1 (13)</td>
<td>1 (13)</td>
<td>3 (38)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>INHL</td>
<td>9</td>
<td>---</td>
<td>---</td>
<td>7 (78)</td>
<td>---</td>
</tr>
<tr>
<td>MCL</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>1 (6)</td>
<td>1 (6)</td>
<td>10 (56)</td>
<td>2 (11)</td>
</tr>
</tbody>
</table>

*Excludes ABCL (n=1, PD) and Other (n=2, SD, PD)

### TTI-621 + Rituximab Combination Therapy

<table>
<thead>
<tr>
<th>N</th>
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<th>SD</th>
<th>ORR Time to Resp</th>
<th>Tmt Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>24</td>
<td>1 (4)</td>
<td>5 (21)</td>
<td>10 (42)</td>
<td>6 (25)</td>
</tr>
<tr>
<td>INHL</td>
<td>4</td>
<td>---</td>
<td>2 (50)</td>
<td>2 (50)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>MCL</td>
<td>3</td>
<td>1 (33)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>1 (3)</td>
<td>8 (26)</td>
<td>12 (39)</td>
<td>9 (29)</td>
</tr>
</tbody>
</table>

*Excludes 3 subjects: ABCL (n=1, SD); PTCL and Other (both NA)

### TTI-621-01: B-Cell NHL Rituximab Combination*

<table>
<thead>
<tr>
<th>N</th>
<th>Response n (%)</th>
<th>Objective Response median days (range)</th>
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</thead>
<tbody>
<tr>
<td>DLBCL</td>
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</tr>
<tr>
<td>8</td>
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<td>5 (21)</td>
</tr>
</tbody>
</table>

*Excludes ABCL (n=1, PD) and Other (n=2, SD, PD)

### TTI-621-01: B-Cell NHL (ABCL/IBCL)*

<table>
<thead>
<tr>
<th>N</th>
<th>Response n (%)</th>
<th>Objective Response median days (range)</th>
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<tbody>
<tr>
<td>DLBCL</td>
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</tr>
<tr>
<td>8</td>
<td>1 (13)</td>
<td>1 (13)</td>
</tr>
</tbody>
</table>

*Excludes ABCL (n=1, PD) and Other (n=2, SD, PD)
TTI-621 Also Exhibits Monotherapy Activity in Patients with T-Cell Lymphoma

- IV monotherapy ORR: 19% in MF (N=21), 25% in PTCL (N=12)
- Intratumoral injections of TTI-621 result in rapid responses

Additional clinical data in MF to be presented at the Saturday poster session (Abstract 1653)

* Injected lesions across 3 lesions
† received TTI-621 + IFNα2a maintenance

Querfeld et al. EORTC CLTF 2018
Does CD47 Blockade Trigger T Cell Responses?

• It is unclear if innate immunity alone is sufficient to produce durable responses in patients
• Preclinical data indicate that CD47 blockade can also promote T cell responses
• Strong evidence that this occurs in patients is currently lacking
• Combinations with T cell checkpoint inhibitors (e.g., anti-PD-1/L1) may be beneficial
Increase in TCR Vβ Clonality Correlates with Clinical Response in a Subject Receiving TTI-621 + Rituximab
Many Questions Remain!

- What is the best format for a CD47 blocking agent?
  - Antibody vs. decoy receptor?
  - Fc isotype?

- What is the mechanism of action in patients?

- What are the best combination partners?
  - Targeted cancer antibodies?
  - T cell checkpoint inhibitors?

- Will next generation CD47 targeting agents provide additional benefit?
  - New CD47 mAbs with greater tumor specificity
  - Bispecific mAbs (e.g., CD47/CD19)
  - Fusions with other immunological agents
  - Anti-SIRPα mAbs
Summary

• CD47 is an important innate checkpoint that restrains macrophage function
• Expression and survival data suggest CD47 is involved in B cell malignancies
• There are multiple types of CD47 blocking agents in clinical development, and many second generation designs in preclinical testing
• Early clinical data using an IgG4 mAb or an IgG1 decoy receptor are very encouraging and suggest that CD47 directed therapy could impact the treatment of B-cell tumors
• Translational/mechanistic studies will be key to understanding the optimal design of CD47 blockers and how they may be used in combination