Clinical Proof-of-Concept of an Anti-CD47 Agent for the Treatment of CTCL: Data from Phase 1 Trials of TTI-621 Employing both Intravenous and Intraleisonal Routes of Administration

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T-Cell Lymphoma Forum 2019: Industry Innovation
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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 and in turn phagocytosis.
- Tumor cells frequently exploit the CD47-SIRPα axis to evade immune surveillance by macrophages.
  - Many hematologic and solid tumors express high levels of CD47.
  - High CD47 expression often correlates with aggressive disease and poor clinical outcomes.
Checkpoint Inhibition Against CD47 May Present Therapeutic Potential For T-Cell Lymphoma

- **High CD47 expression in Sézary Cells**
  - Median Fl
  - $p < 0.0001$

- **CD47 levels correlated to survival of patients with Sézary Syndrome**
  - $p < 0.01$

- **Anti-CD47 Ab induces longer survival in transformed CTCL PDX (DFTL 22685)**

- **Anti-CD47 mAb efficacy is macrophage and not neutrophil dependent in a TCL PDX model**

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Akilov et al. 2017 EORTC CLTF

TTI-621: A Dual Function SIRPαFc Decoy Receptor that Blocks CD47 and Delivers an Activating Signal

- Blocks the CD47 DO NOT EAT signal
- Delivers an EAT signal through FcγRs
- Macrophage Phagocytosis
- Antigen Presentation & Adaptive Immunity

CD47 binding domain of human SIRPα

Human IgG1
TTI-621 IgG1 Fc delivers a potent “eat” signal

CD47 Blocker* (Company) | Isotype
---|---
TTI-621 (Trillium) | IgG1
TTI-622 (Trillium) | IgG4
Hu5F9 (Forty Seven) | IgG4
CC-90002 (Celgene) | IgG4
SRF231 (Surface Oncology) | IgG4
ALX148 (ALX Oncology) | Inert IgG1

*Clinical stage compounds

Advantages of an IgG1 Fc:

- Maximizes potency by delivering an activating signal to macrophages through Fc receptors
- Higher likelihood of monotherapy activity - not dependent upon a combination with another IgG1 antibody
- Could be used to treat tumors where no anti-cancer antibody is available
TTI-621 Does Not Bind Human RBCs

Advantages of non-RBC binding:
• Minimizes likelihood of anemia
• Avoids drug removal by the “antigen sink”
• Avoids interference with transfusion medicine testing

Why does TTI-621 not bind RBCs?
• Moderate binding affinity – need bivalent interaction
• Lack of CD47 mobility in the RBC membrane prevents clustering and limits bivalent binding

CD47 is associated with the Rh Ag complex and anchored to the cytoskeleton in RBCs


Salomao et al. PNAS 2008
Multicenter, open-label phase 1 study in patients with relapsed/refractory hematologic malignancies (NCT02663518)

**Dosing**
- Monotherapy Indications
  - Lymphoma
  - Identified initial MTD (0.2 mg/kg) based on conservative DLT criteria

**Initial Expansion**
- Heme Malignancies
  - CD20+ NHL (Rituximab)
  - cHL (Nivolumab)
- 0.2 mg/kg (mono)
- 0.1 mg/kg (combo)

**Focused Expansion**
- CTCL, PTCL
- 0.2 to 0.5 mg/kg (Dose Ramp-up)

**Combination Indications**

**Dose Escalation**
- Dose Escalation (0.05, 0.1, 0.2, 0.3 mg/kg)

**Ongoing**
- Dose Intensification at Investigator Discretion Made Permissible per Protocol Amendment
- Simon's 2-stage Design
Intravenous TTI-621 is Well Tolerated

- Most frequent AEs were low-grade infusion reactions, clinically managed by pre-medication and close monitoring
- ≥ Grade 3 thrombocytopenia occurred in 18% patients
- Diverse patient population from the following expansion cohorts: AML, MDS, MPN, B-NHL, T-NHL, HL, MM, CLL, SCLC

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Cohort(s): All</th>
<th>Total n=179</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion Related Reaction</td>
<td>69 (39)</td>
<td>72 (40)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (6)</td>
<td>44 (25)</td>
</tr>
<tr>
<td>Chills</td>
<td>34 (19)</td>
<td>34 (19)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27 (15)</td>
<td>27 (15)</td>
</tr>
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</tr>
<tr>
<td>Fatigue</td>
<td>27 (15)</td>
<td>27 (15)</td>
</tr>
<tr>
<td>Nausea</td>
<td>21 (12)</td>
<td>21 (12)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>8 (4)</td>
<td>20 (11)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18 (10)</td>
<td>18 (10)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>16 (9)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (8)</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13 (7)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (7)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>7 (4)</td>
<td>9 (5)</td>
</tr>
</tbody>
</table>

Source: 28 Nov 2018 DDLs

Based on Snapshot data, Nov. 26, 2018
Transient Thrombocytopenia 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 – 1/179 patients had dosing discontinued due to thrombocytopenia

Based on Snapshot data, Nov. 26, 2018
Dose Intensification is Well Tolerated

- Dose intensification at Investigator’s discretion allowed per protocol; later standardized in Amendment 8 (Ramp up from 0.2 to 0.5 mg/kg within 5 weeks)

- Included in this analysis were 22 patients dose intensified; 15 dose intensified to 0.5 mg/kg between Week 5-30.

- No worsening of post-dose platelet decrease was observed at 0.5 mg/kg

- No apparent differences in other AEs were seen between patients receiving stable dose of 0.2 mg/kg and patients dose intensified on study

Based on Snapshot Data, Nov. 26, 2018
IV TTI-621 Has Single Agent Activity in T-Cell Lymphoma Patients

- Monotherapy ORR by the data cut: 17% in MF, 20% SS, and 18% in PTCL
- 5/7 responses observed in patients receiving weekly doses of 0.2 mg/kg
- One Sezary patient achieved CR after 48 weeks of study treatment, showing the possibility of a slow response to the study drug.

<table>
<thead>
<tr>
<th>TTI-621-01: T-Cell Lymphoma</th>
<th>N</th>
<th>Response n(%)</th>
<th>Objective Response (days) med (range)</th>
<th>Time to Response</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CR</td>
<td>PR</td>
<td>Total</td>
<td>CR</td>
</tr>
<tr>
<td>Mycosis Fungoides</td>
<td>24</td>
<td>---</td>
<td>4 (17)</td>
<td>4 (17)</td>
<td>49 (23-51)</td>
</tr>
<tr>
<td>Sezary Syndrome</td>
<td>5</td>
<td>1 (20)</td>
<td>---</td>
<td>1 (20)</td>
<td>336 (336-336)</td>
</tr>
<tr>
<td>Peripheral TCL</td>
<td>11</td>
<td>---</td>
<td>2 (18)</td>
<td>2 (18)</td>
<td>50 (20-79)</td>
</tr>
<tr>
<td>Total / Overall</td>
<td>40</td>
<td>1 (3)</td>
<td>6 (15)</td>
<td>7 (18)</td>
<td>50 (20-336)</td>
</tr>
</tbody>
</table>

Based on Snapshot data, Dec. 26, 2018
Intratumoral Administration Study (TTI-621-02)

Multicenter, open-label phase 1 study of direct intratumoral injection of TTI-621 in patients with relapsed/refractory mycosis fungoides (MF) or percutaneously accessible solid tumors (NCT02890368)

• Advantages of direct injection:
  • Obtain very high local drug concentrations
  • Avoid systemic antigen sink
  • Rapid responses

*10 mg 3x/wk for 2 wks then 10 mg weekly
^Combinations: IFN-α, anti-PD-1/PD-L1, T-vec (melanoma only), radiation (plasmacytoma only)
Intralesional TTI-621 Injections Were Well Tolerated in CTCL Patients

- Related adverse events (AEs) all Grade 1 or 2; no Grade ≥3 AEs
- Common related AEs include chills, injection site pain, and fatigue
- No related serious adverse events or dose-limiting toxicity

### Related Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 1-2</th>
<th>Grade ≥ 3</th>
<th>Total* (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event</td>
<td>19 (70)</td>
<td>0</td>
<td>19 (70)</td>
</tr>
<tr>
<td>Chills</td>
<td>8 (30)</td>
<td>0</td>
<td>8 (30)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>8 (30)</td>
<td>0</td>
<td>8 (30)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (22)</td>
<td>0</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Erythema</td>
<td>3 (11)</td>
<td>0</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (11)</td>
<td>0</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (7)</td>
<td>0</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (7)</td>
<td>0</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (7)</td>
<td>0</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (7)</td>
<td>0</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

* TEAEs in 1 subject, each: arthralgia, decreased appetite, dizziness, flatulence, flushing, hyperhidrosis, inflammation, influenza like illness, insomnia, local swelling, mycosis fungoides lesional swelling, neutrophil count increased, edema, pain, palpitations, penile swelling, pruritus, pruritus generalised, thrombocytopenia, uncoded, white blood cell count increased.

Querfeld et al. ASH 2018
CAILS Reductions in Injected Lesions Were Observed in the Majority of Patients

CAILS scores were available in 22 patients:
- 20 (91%) patients had decreased CAILS scores.
- 9 (41%) patients had a reduction in CAILS scores by ≥ 50%.
- CAILS score reductions occurred at all dose levels, following single and multiple injections, in all stages (IA to IVB), and in all lesion types (plaques, tumors, etc.).

*Composite Assessment of Index Lesion Severity, a measure of local lesion responses

Querfeld et al. ASH 2018
Systemic Effects Were Observed in One Patient Receiving Continuation Monotherapy

- Rapid resolution was observed of the injected lesion on the calf and of distal, non-injected lesions on abdomen, left flank/back and arms.
- CAILS reductions were observed in the initially injected target lesions (blue) and additional lesions injected at later time points (red).

Querfeld et al. ASH 2018
Local-Regional Responses Were Observed in Non-Injected, Adjacent Control Lesions

- 9 patients with reduced CAILS had a paired CAILS assessments in an adjacent non-injected lesion
- Injected lesion CAILS decreased -6% to -95% in all patients
- Non-injected lesions CAILS decreased -12% to -67% in 7/9 patients
- Median distance between paired injected and non-injected lesions is estimated to be 5.3 cm (range 0.2 – 15+ cm)
Peripheral Responses Were Observed Following Local Injections

Single 1 mg Injection

Single 1 mg Injection

Single 3 mg Injection
Summary

• TTI-621 is a novel dual function decoy receptor that blocks the CD47 “do not eat” signal and delivers an activating signal through FcRs

• TTI-621 is differentiated from other CD47 blocking agents by its potent IgG1 Fc and lack of RBC binding

• Intratumoral delivery of TTI-621 has been shown to be well tolerated and results in responses in injected and non-injected MF lesions

• Intravenous TTI-621 is well tolerated, activity observed as a single agent in CTCL, PTCL and DLBCL (Not shown) patients and in combination with rituximab in DLBCL patients (not shown) at relatively low doses; dose intensification ongoing

• Clinical POC of TTI-621 has been demonstrated for the treatment of CTCL from IV and IL drug delivery route

• Clinical program is moving forward in three distinct areas:
  • Intratumoral mono- and combination-therapy in CTCL
  • IV monotherapy in both CTCL and PTCL
  • IV combination therapy in B-cell lymphoma
Acknowledgements

- Patients and their families
- Staff members who contributed to the TTI-621 clinical studies:
  - BC Cancer Agency
  - City of Hope
  - Cleveland Clinic
  - Colorado Blood Cancer Institute
  - Columbia University
  - Hackensack University Medical Center
  - Mayo Clinic – Rochester
  - Mayo Clinic - Jacksonville
  - Memorial Sloan Kettering Cancer Center
  - New York University
  - Oregon Heath & Sciences University
  - Princess Margaret Hospital
  - Seattle Cancer Care Alliance
  - Stanford University
  - Tennessee Oncology
  - University of Pittsburg
Trillium Therapeutics Inc. (NASDAQ/TSX:TRIL) is an immuno-oncology company dedicated to the discovery & development of novel and innovative cancer therapies
CAILS Responses Occurred Rapidly Within the 2-Week Induction Period

Rapid and sustained reductions in CAILS scores were observed following both single and multiple injections in patients who only received induction therapy of ≤2 weeks.