TTI-621 (SIRPαFc): A Checkpoint Inhibitor of the Innate Immune System that Blocks the CD47 “Do Not Eat” Signal

Bob Uger, PhD
Chief Scientific Officer

24th International Molecular Medicine Tri-Conference: Cancer Immunotherapy
This presentation may contain forward-looking statements, which reflect Trillium's current expectation regarding future events. These forward-looking statements involve risks and uncertainties that may cause actual results, events or developments to be materially different from any future results, events or developments expressed or implied by such forward-looking statements. Such factors include, but are not limited to, Trillium's ability to obtain financing to advance the products in its development portfolio; changing market conditions; the successful and timely completion of pre-clinical and clinical studies; the establishment of corporate alliances; the impact of competitive products and pricing; new product development risks; uncertainties related to the regulatory approval process or the ability to obtain drug product in sufficient quantity or at standards acceptable to health regulatory authorities to complete clinical trials or to meet commercial demand; and other risks detailed from time to time in Trillium's ongoing quarterly and annual reporting. Forward-looking statements are made only as of the date of this presentation and except as required by applicable securities laws, Trillium undertakes no obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise.
Many Tumor Cells Use the CD47 “Do Not Eat” Signal to Inhibit Macrophage Phagocytosis

Tumors known to express high levels of CD47

- Acute myeloid leukemia
- Acute lymphoblastic leukemia
- Chronic lymphocytic leukemia
- Chronic myeloid leukemia
- Diffuse large B cell lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Marginal zone lymphoma
- Multiple myeloma
- Myelodysplastic syndrome
- Bladder cancer
- Breast cancer
- Colon cancer
- Esophageal cancer
- Gastric cancer
- Glioblastoma
- Glioma
- Kidney cancer
- Leiomyosarcoma
- Liver cancer
- Lung cancer
- Melanoma
- Ovarian cancer
- Pancreatic cancer
- Prostate cancer

In many cases high CD47 expression correlates with aggressive disease and poor clinical outcomes
TTI-621: A Dual Function SIRPαFc Decoy Receptor

CD47 binding domain of human SIRPα

Blocks the DO NOT EAT signal from CD47

Human IgG1 Fc

Delivers an EAT signal to macrophages through FcγRs

**TTI-621 is a dual function decoy receptor that blocks the suppressive CD47 signal while engaging activating Fc receptors**
TTI-621 Activates Both the Innate and Adaptive Immune Systems

CD47 inhibits macrophage phagocytosis

SIRPαFc binds to CD47

SIRPαFc triggers activating FcyRs on macrophages

Phagocytosis may lead to antigen presentation and activation of the adaptive immune system

©Audra Geras
TTI-621 Enables Macrophages to Phagocytose A Broad Array of Human Tumor Cells \textit{In Vitro}

**TTI-621 In Vitro Activity:**
- Dose-dependent increase in phagocytosis
- Mean EC$_{50} = 10$ nM (767 ng/mL)
- Active against a broad range of hematologic and solid tumors
- Activates phagocytosis by M1 and M2 macrophages

![Control Fc (1 μM) vs. TTI-621 (1 μM)]

![Representative phagocytosis data (AML target)]

![Activity against primary hematologic tumor samples]
TTI-621 Triggers Phagocytosis of Tumor Cells by All Macrophage Subsets

Phagocytosis of a DLBCL cell line (Toledo) by polarized human macrophages
CD47 Blockade by TTI-621 Activates Both the Innate and Adaptive Immune Systems

Increased tumor cell phagocytosis by TTI-621 leads to enhanced antigen presentation and T cell proliferation using a model (CMV) antigen system.
Assessing TTI-621 Activity *in Vivo*

Xenografts in NOD.SCID mice: the “gold standard” model in AML

1. AML cells from cancer patient
2. Intrafemoral injection
3. NOD.SCID mouse
4. Irradiate
5. Anti-CD122 mAb
6. TTI-621
7. Isolate bone marrow (injected and non-injected) & spleen
8. Measure leukemia by flow cytometry
TTI-621 is Highly Potent *in Vivo*

**TTI-621 In Vivo Activity:**
- Active across a range of xenograft models
- Activity in the AML xenograft model at 0.05 mg/kg/wk HED*
- Similar potency observed with a mouse surrogate SIRPαFc (in presence of antigen sink)
- In non-human primate studies, no severe toxicity occurs up to an HED of 0.3 mg/kg/week

Intra-femoral injection of AML patient tumor cells
TTI-621 dosed at 8 mg/kg IP 3x/wk for 4 wks starting 14d after engraftment

Results suggest a potent effect at 0.05 mg/kg HED and the presence of a therapeutic window for efficacy
Maximizing Anti-Tumor Activity using an IgG1 Fc

Intra-femoral injection of AML patient tumor cells

SIRPαFc dosed at 8 mg/kg IP 3x/wk for 4 wks starting 21d after engraftment
Minimal Binding to RBCs Differentiates TTI-621 From CD47-Specific Antibodies

- CD47 is highly expressed by RBCs, leading to concerns about toxicity (anemia) and poor pharmacokinetics (antigen sink)
- Unlike CD47 antibodies, TTI-621 binds only minimally to human RBCs
- This low binding to RBCs has several potential advantages:
  - Lower risk of anemia
  - Avoidance of the RBC antigen sink
  - Non-interference with blood typing tests
The Presence of Detergent-Insoluble CD47 in RBC Membranes Correlates with Low SIRPαFc Binding

We hypothesize that the lack of CD47 membrane mobility combined with moderate affinity of TTI-621 for target results in a lack of human RBC binding
TTI-621 Phase 1 Study in Patients with Advanced Hematological Malignancies

Phase 1a: Dose Escalation
Lymphoma

Phase 1b: Expansion
Acute Myeloid Leukemia
Myelodysplastic Syndrome
Chronic Lymphocytic Leukemia
Hodgkin Lymphoma
Indolent B Cell Lymphoma
Aggressive B Cell Lymphoma
T Cell Lymphoma
Multiple Myeloma
Myeloproliferative Neoplasms
CD20+ Lymphoma with rituximab

- Standard 3+3 dose escalation in lymphoma patients; Expansion across a range of heme malignancies (NCT02663518)
- 6 US Phase 1a sites:
  - City of Hope, Duarte CA
  - Colorado Blood Cancer Institute, Denver CO
  - Tennessee Oncology, Nashville TN
  - Columbia University, New York NY
  - Mayo Clinic, Rochester MN
  - Memorial Sloan Kettering Cancer Center, New York, NY
- Phase 1b is currently enrolling, additional sites (US and Canada) are now being added
- Data from Phase 1a (18 patients) provided at ASH 2016
TTI-621 Phase 1a Results

Safety

- Drug generally well-tolerated
- No induced anemia
- Transient, dose-dependent thrombocytopenia (an anticipated, on-target effect)
- Defined MTD: 0.2 mg/kg/wk

Pharmacodynamics

- Achieved receptor occupancy levels that correlate with drug activity in vitro
- Observed elevations in macrophage-associated chemokines (MIP-1α, MIP-1β) that are associated with TTI-621 activity in vitro

Anti-tumor activity

- One patient (Hodgkin lymphoma) achieved a transient partial response
- Several patients experienced prolonged progression-free intervals characterized by decreasing tumor volume and decreasing PET activity

*We believe these data provide preliminary evidence that TTI-621 is active as a monotherapy in patients with relapsed/refractory lymphomas*
TTI-621 is Generally Well Tolerated

<table>
<thead>
<tr>
<th>All Adverse Events* (N=18)</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion-related reaction</td>
<td>11 (61%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (50%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (39%)</td>
<td>1 (6%)†</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (28%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 (22%)</td>
<td>1 (6%)†</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Chills</td>
<td>3 (17%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (17%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>3 (17%)</td>
<td>3 (17%)</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (17%)</td>
<td>1 (6%)†</td>
<td>-</td>
</tr>
<tr>
<td>Back pain</td>
<td>2 (11%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cough</td>
<td>2 (11%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (11%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (11%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (11%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (11%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (11%)</td>
<td>1 (6%)†</td>
<td>-</td>
</tr>
</tbody>
</table>

*Adverse events of any causality in ≥2 patients †Unrelated self-limited gastroenteritis in 1 patient
Transient Thrombocytopenia is Consistently Observed
The Level of Receptor Occupancy on Peripheral Leukocytes at the Expansion Dose is Associated with High Phagocytosis Activity \textit{In Vitro}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{graph.png}
\caption{Peak (end of infusion) CD47 occupancy assessed on peripheral leukocytes from patients dosed with TTI-621.}
\end{figure}

\textit{Phagocytosis vs. occupancy in vitro using hematologic tumor cell lines and human macrophages}
The Chemokines MIP-1α and MIP-1β are Increased After TTI-621 Infusion and Correlate with *In Vitro* Macrophage Phagocytosis
Decreasing Tumor Volume and/or Reduced Metabolic Activity Over Extended Intervals of Continued Dosing Observed in Some Patients
TTI-621 Phase 1 Study in Patients with Solid Tumors and Mycosis Fungoides (T cell lymphoma)

- Phase 1 study of intratumoral TTI-621 in patients with percutaneously accessible solid tumors or mycosis fungoides (NCT02890368)

- Rationale for intratumoral route of administration:
  - Compelling preclinical efficacy in xenograft models
  - Achieve high local target saturation
  - Can perform serial, on-treatment biopsies to characterize the effects of TTI-621 on the tumor microenvironment (e.g., macrophages, T cells)

- FDA clearance in Q3/16; Expect first patient dosed in Q1/2017

- Plan to provide update 2H/2017

DLBCL (Toledo) xenograft model
TTI-621 intratumoral injections (0.2 mg/mouse, arrowheads)
Expanding our CD47 Pipeline with TTI-622

- **TTI-621** is the most potent SIRPαFc format
- **TTI-622** is less likely to deplete platelets, enabling higher exposures
- Both agents may have unique combination opportunities
- Both agents are differentiated from antibodies by a lack of binding to human erythrocytes

**TTI-621**

- Human SIRPα
- Human IgG1 Fc

Blocks CD47 and delivers a strong activating signal through FcγRs

**TTI-622**

- Human SIRPα
- Human IgG4 Fc

Blocks CD47 and delivers a modest activating signal through FcγRs
TTI-621 – Broad Clinical Effort in Multiple Malignancies

**TTI-621-01 Trial:**
- Continue assessment of 0.2 mg/kg weekly dose across a range of hematologic malignancies (additional cohorts expected)
- Explore combinations with monoclonal antibodies and other anti-cancer agents
- Determine if greater exposures can be achieved through alternative dosing strategies

**TTI-621-02 Trial:**
- Probe the biological effects of TTI-621 on the tumor microenvironment following intratumoral administration
- Explore combinations with monoclonal antibodies and other anti-cancer agents

**TTI-622:**
- Submit IND by year end 2017
Acknowledgments

University Health Network, Toronto, ON
John Dick
Jean Wang

The Hospital for Sick Children, Toronto, ON
Jayne Danska

University of Western Ontario, London, ON
James Koropatnick
Saman Maleki

Trillium Therapeutics
Research and Clinical staff

Mayo Clinic, Rochester, MN
Stephen Ansell

City of Hope, Duarte, CA
Robert Chen

Tennessee Oncology, Nashville, TN
Ian Flinn

Colorado Blood Cancer Institute, Denver, CO
Michael Maris

Columbia University Medical Center, New York, NY
Owen O’Connor

Patients and their families
Trillium Therapeutics Inc. (NASDAQ/TSX:TRIL) is an immuno-oncology company dedicated to the discovery and development of novel and innovative cancer therapies.