A Phase 1 Dose-escalation Trial of Intratumoral TTI-621, a Novel Immune Checkpoint Inhibitor Targeting CD47, in Subjects With Relapsed or Refractory Percutaneously-accessible Solid Tumors and Mycosis Fungoides

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Introduction

- Tumors exploit the CD47-SIRPα (“do not eat”) interaction to evade macrophage-mediated phagocytosis
- TTI-621 (SIRPαFc) is a novel immune checkpoint inhibitor that blocks the CD47 “do not eat” signal and engages activating FcγR on macrophages via its IgG1 Fc region
- TTI-621 has been well-tolerated and is associated with anti-tumor activity in a concurrent trial of intravenous dosing (NCT02663518)
- This ongoing Phase 1a/b trial will assess the safety, MTD, and antitumor activity of intratumoral administration of TTI-621 in subjects with relapsed/refractory solid tumors and mycosis fungoides (NCT02890368)

Two-Part Open-Label Phase 1 Study in R/R Solid Tumors and Mycosis Fungoides

- Escalation phase to establish MTD:
  - Dose Escalation: 1, 3, and 10 mg/injection
  - Injection Frequency: Single injection up to 6 injections over 2 weeks
- Expansion phase to test established MTD and frequency with injection of single and multiple lesions
- Primary endpoints: incidence and severity of adverse events
- Secondary endpoints: PK, PD, anti-drug antibody, objective response and duration of response

Immune Monitoring and Pharmacodynamics

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Analysis Method</th>
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<td>Are there changes in the peripheral immune compartment?</td>
<td>Phenotyping of adaptive and innate cell subsets by flow cytometry and NanoString PanCancer Immune Profiling Panel</td>
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<td>Is there a change in Tumor Infiltrating Lymphocytes following TTI-621 injection?</td>
<td>T cell receptor Vβ sequencing from pre- and post-treatment biopsy samples</td>
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<td>Are there changes in peripheral cytokines and chemokines associated with TTI-621 activity?</td>
<td>Multiplex immunoassay and ELISA</td>
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<td>Are there changes in the tumor microenvironment, including: macrophage content and CD8+ cell infiltration?</td>
<td>NanoString PanCancer Immune Profiling Panel and multiplex immunohistochemistry of injected and adjacent lesions at multiple timepoints</td>
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<td>Do polymorphisms in FcγR or other genes affect response?</td>
<td>Exon sequencing of CD47, SIRPα, and FcγR (CD16, CD32, and CD64)</td>
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Supporting Preclinical Data

Weekly intratumoral administration of TTI-621 (0.2 mg/mouse, arrowheads) controls tumor growth and promotes survival in a DLBCL (Toledo) xenograft model

Conclusions

- TTI-621 has the potential to directly increase tumor-specific phagocytosis and antigen presentation, leading to durable T cell responses and systemic anti-tumor immunity
- Intratumoral injection should achieve high local concentrations of TTI-621
- Comprehensive PK/PD assessments with serial biopsies should elucidate the effects of TTI-621 on the tumor microenvironment

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