Intralesional Administration of the CD47 Antagonist TTI-621 (SIRPαFc) Induces Responses in Both Injected and Non-injected Lesions in Patients with Relapsed/Refractory Mycosis Fungoides and Sézary Syndrome: Interim Results of a Multicenter Phase I Trial

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BACKGROUND
CD47 is an immune checkpoint that binds signal regulatory protein alpha (SIRPα) and delivers a “do not eat” signal to suppress macrophage phagocytosis. Tumor cells, including T-cell lymphomas, frequently overexpress CD47 to escape immune surveillance. TTI-621 (SIRPαFc) is a fusion protein consisting of the CD47 binding domain of human SIRPα linked to the Fc region of human IgG1, designed to enhance phagocytosis and antitumor activity by blocking the CD47-SIRPα interaction between malignant cells and macrophages, and engaging activating Fc receptors (Figure 1). It is hypothesized that direct intraluminal (iL) administration of TTI-621 may enhance both local and systemic antitumor activity.

RESULTS
Patients
- At the data cut-off (Nov 5, 2018), 27 patients with CTCLs were enrolled: MF (n=22), MF with transformation (n=3), primary cutaneous anaplastic large cell lymphoma (pALCL) (n=1), and Sézary Syndrome (SS) (n=1).
- Demographic and baseline disease characteristics are shown in Table 2.

Efficacy
- Overall CAILS scores were available in 22 patients (Figure 1).
- 9 (41%) patients had a reduction in CAILS scores by a 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.).
- 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 (Figure 2).

Individual Responses
- Five patients received weekly continuation monotherapy with TTI-621 beyond the 2 week induction period (ranging 1-26 weeks of further treatment). 4/5 have available continuation therapy CAILS scores, of which 3 patients saw further reductions with continued treatment (-18% to -100%). Resolution of lesions in one patient is shown in Figure 4. 4. Response with continued Weekly TTI-621

CONCLUSIONS
- Single and multiple IL injections of up to 10 mg TTI-621 were well tolerated. 91% (9/10) of heavily pre-treated MF/SS patients had a reduction in CAILS scores in treated lesions; 41% (9/22) had ≥50% CAILS score decrease.
- Responses were rapid and occurred across all disease stages following single and multiple TTI-621 injections of varying doses.
- Similar CAILS-based changes were seen in adjacent non-injected lesions, suggesting local regional effects that were not confined to the site of injection.
- Continuation monotherapy led to further reductions in CAILS scores in 3/4 evaluable patients and evidence of systemic effects in one patients, suggesting that beyond the week 2 induction and rolling injections may provide additional clinical benefit.
- Initial experience suggests a possible benefit to combining TTI-621 with PEG-IFN-α2a.
- Emerging translational data demonstrating that IL TTI-621 administration leads to a rapid influx of macrophages and CD8+ T-cells.

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STUDY TTI-621-02
A multicenter, open-label Phase I study to characterize the safety, tolerability, pharmacokinetics, pharmacodynamics and antitumor activity of IL injections of TTI-621 (NCT02890368) in adult patients with relapsed/refractory (R/R) permeatably accessible solid tumors and mycosis fungoides (MF).

Study Design and Methods
Eligible patients were adults with R/R permeatably accessible solid tumors and MF who had previously progressed on standard anticancer therapy or for whom no other approved therapy existed.

Dose Escalation was based on a modified 3+3 scheme escalating doses sequentially through predefined levels of 1, 3, and 10 mg per injection. Injection frequency was also sequentially increased from single injections through 6 injections administered over 1 or 2 weeks (see Table 1).

Dose Expansion testing of the maximally assessed TTI-621 dose and schedule proceeded with six 10 mg doses administered four times over 2 weeks (induction therapy), in each of 6 cohorts testing both single agent and combination treatments (PD-1/PD-L1 inhibitor, pegylated IFN-α2a, T-Vxx, radiation).

Weekly Continuation Therapy beyond the initial 2 week induction therapy at investigator’s discretion was recently incorporated into the study by a protocol amendment. Additional lesions can be injected beyond the 3 target lesions identified in induction therapy (rolling injections).

Composite Assessment of Index Lesion Severity (CAILS) scores for injected and non-injected lesions were assessed at the end of induction therapy and at later time points in some subjects. Serial biopsies were collected to assess impact of TTI-621 on the tumor microenvironment.