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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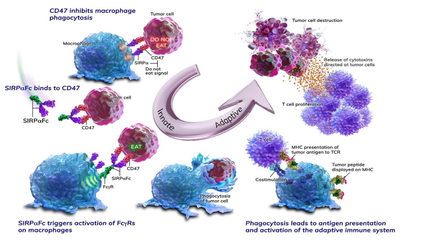
BACKGROUND

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 Fcγ receptors (Figure 1). It is hypothesized that direct intralesional (IL) administration of TTI-621 may enhance both local and systemic antitumor activity.

Figure 1. TTI-621 Activates both the Innate and Adaptive Immune Systems



STUDY TTI-621-02

A multicenter, open-label Phase 1 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) percutaneously accessible solid tumors and mycosis fungoides (MF).

Study Design and Methods

Eligible patients were adults with R/R percutaneously 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 3 or 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 MWF 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-Vec, 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.

Study Schema and Enrollment

Table 1. Study Schema and Enrollment

		Cohorts	mg per Injection#	Injection Frequency	Lesions Injected	Total n=42	CTCL n=27(*)
Escalation	1	Single Lesion/Single Injection	1	Single	1	3	2
	2	Single Lesion/Single Injection	3	Single	1	3	1
	3	Single Lesion/Single Injection	10	Single	1	3	3
	4	Single Lesion/Multiple Injections	10	MWF x 1 Wk	1	3	1
	5	Single Lesion/Multiple Injections	10	MWF x 2 Wks	1	6	5
Expansion	6	Single Lesion Expansion	10	MWF x 2 Wks	1	11	5
	7	Multiple Lesions Expansion	10	MWF x 2 Wks	≤ 3	10	9 (5)
	8	+ PD-1/PD-L1 Inhibitor	10	MWF x 2 Wks	≤ 3	2	0
	9	+ PEG-IFN-α2a	10	MWF x 2 Wks	≤ 3	1	1 (1)
	10	+ T-Vec	10	MWF x 2 Wks	≤ 3	0	0
	11	+ Radiation	10	MWF x 2 Wks	≤ 3	0	0

dose injected in a total volume of 1 ml either into a single lesion or distributed over a maximum of 3 lesions
* (n) - continued weekly injections beyond initial 2-week induction therapy

RESULTS

Patients

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

Table 2. Demographic and Baseline Disease Characteristics

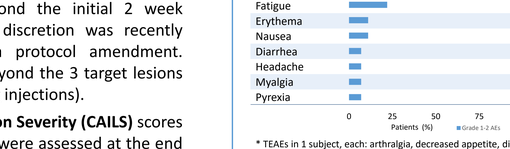
Baseline Characteristics CTCL Subjects	Total n=27
Median Age, years (min-max)	62 (32-85)
Male, n (%)	21 (78)
ECOG PS 0-1, n (%)	26 (96)
Primary Diagnosis, n (%)	
MF	22 (81)
MF with Transformation	3 (11)
pcALCL	1 (04)
Sézary Syndrome	1 (04)
Overall Stage at Study Entry, n (%)	
IA	4 (15)
IB	4 (15)
IIA	1 (04)
IIB	15 (56)
IVA	2 (07)
IVB	1 (04)
Prior Therapy, n (%)	
Local and/or Systemic	27 (100)
Local and Systemic	13 (48)
Median Lines of Prior Treatment, (min-max)	
Systemic	3 (0-16)

Safety

- All treatment-related AEs were Grade 1 or 2 in severity.
- No treatment-related SAEs or dose-limiting toxicity were observed (Table 3).

Table 3. Related Adverse Events in ≥ 2 Patients

Related Adverse Events n (%)	Grade 1-2	Grade ≥ 3	Total* (N=27)
Any Adverse Event	19 (70)	0	19 (70)
Chills	8 (30)	0	8 (30)
Injection site pain	8 (30)	0	8 (30)
Fatigue	6 (22)	0	6 (22)
Erythema	3 (11)	0	3 (11)
Nausea	3 (11)	0	3 (11)
Diarrhea	2 (7)	0	2 (7)
Headache	2 (7)	0	2 (7)
Myalgia	2 (7)	0	2 (7)
Pyrexia	2 (7)	0	2 (7)

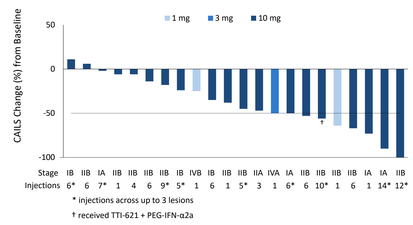


* TEAEs in 1 subject, each: arthralgia, decreased appetite, dizziness, flatulence, flushing, hyperhidrosis, inflammation, influenza like illness, insomnia, local swelling, mycosis fungoides lesional swelling, neutrophil count increased, edema, pain, palpitations, penile swelling, pruritus, pruritus generalised,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

Efficacy

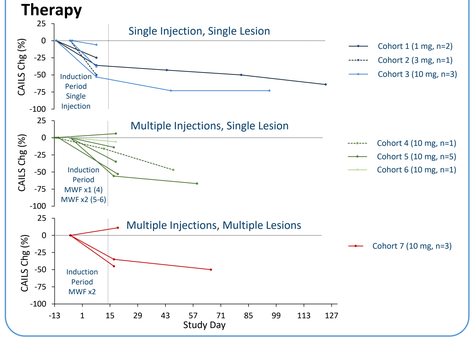
- Overall CAILS scores were available in 22 patients (Figure 1).
  - 20 (91%) patients had decreased CAILS scores.
  - 9 (41%) patients had a reduction in CAILS scores by ≥ 50%.
  - CAILS score reductions occurred at all dose levels, following single and multiple injections, in all stages (IA to IVB), and in all lesion types (plaques, tumors, etc.).

Figure 1. CAILS Scores by Response



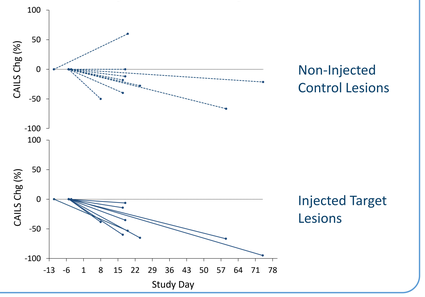
- Rapid and sustained reductions in CAILS scores were observed following both single and multiple injections in patients who only received induction therapy of ≤2 weeks (Figure 2).

Figure 2. CAILS Scores in Patients Receiving Only Induction Therapy



- Nine patients with reduced CAILS scores had a paired CAILS assessment in an adjacent non-injected lesion (Figure 3).
  - Injected lesion CAILS scores decreased -6% to -95% in all nine patients.
  - Non-injected lesion CAILS scores decreased -12% to -67% in 7/9 patients, suggesting a local regional effect of TTI-621 that is not limited to the site of injection.
  - The median distance between paired injected and non-injected lesions was estimated to be 5.5 cm (range 0.2 - 15+ cm).

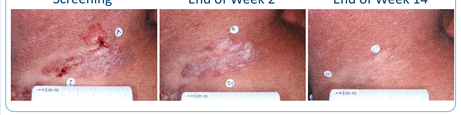
Figure 3. CAILS in Injected vs Non-Injected Control Lesions



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.

Figure 4. Response with Continued Weekly TTI-621

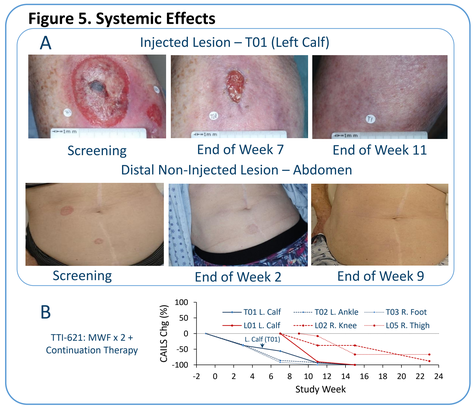


* photo taken prior to study treatment but after the baseline biopsy

Stage IA MF patient with complete resolution of both Injected (I) and adjacent non-injected (A) lesions after 14 weeks of TTI-621

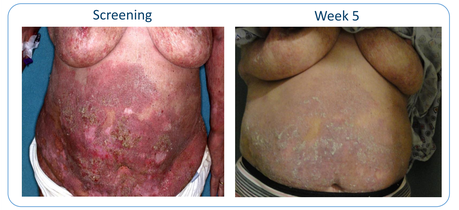
- Systemic effects were seen in one patient with MF with transformation receiving continuation monotherapy and rolling injections (Figure 5). Rapid resolution was observed of the injected lesion on the calf (Figure 5A, upper panel), and of distal, non-injected lesions on abdomen (Figure 5A, lower panel), left flank/back and arms (not shown).
- CAILS score reductions were observed in the initially injected target lesions (blue, Figure 5B) and additional lesions injected at later time points (red, Figure 5B).

Figure 5. Systemic Effects



- TTI-621 + PEG-IFN-α2a resulted in more rapid systemic effects than expected for PEG-IFN-α2a alone (Figure 6).

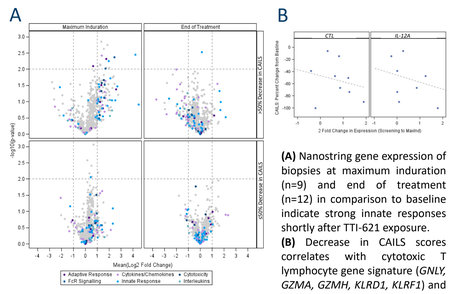
Figure 6. Rapid Systemic Effects with TTI-621 + PEG-IFN-α2a



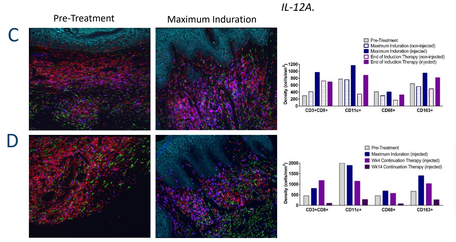
TTI-621: Multiple 10 mg Injections MWF x 2 (Week 1-2)
PEG-IFN-α2a: Two 90 mg Injections (Weeks 3-4)

Translational Assessments

Figure 7. Gene Expression and IHC Analysis Indicate Rapid Innate and Adaptive Responses



(A) Nanostring gene expression of biopsies at maximum induration (n=9) and end of treatment (n=12) in comparison to baseline indicate strong innate responses shortly after TTI-621 exposure. **(B)** Decrease in CAILS scores correlates with cytotoxic T lymphocyte gene signature (*GNLY, GZMA, GZMH, KLRD1, KLRF1*) and *IL-12A*.



TTI-621 injection increases CD8+ T cells, DC, and macrophages. **(C)** Representative images from biopsies of injected lesions from the subject in Figure 4 at pre-treatment and maximum induration. Immune infiltrate density was determined for both injected and non-injected lesions at maximum induration and end of induction therapy. **(D)** Representative images from biopsies of injected lesions from the subject in Figure 5 at pre-treatment and maximum induration. Immune infiltrate density was determined for available biopsies up to week 14 of continuation therapy.

CONCLUSIONS

- Single and multiple IL injections of up to 10 mg TTI-621 were well tolerated.
- 91% (20/22) of heavily pretreated 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 patient, suggesting treatment beyond the two-week 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 demonstrate that IL TTI-621 administration leads to a rapid influx of macrophages and CD8+ T cells.

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