TTI-621 in Patients With R/R Hematologic Malignancies

Clinical Trials: Targeted Therapy

Phase 1 Study of the CD47 Blocker TTI-621 in Patients with Relapsed or Refractory Hematologic Malignancies


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Statement of Translational Relevance

CD47 blockade, targeting a key innate immune checkpoint, is a promising therapeutic strategy in immuno-oncology. TTI-621 (SIRPα-IgG1 Fc), a novel IgG1-based CD47-blocking Fc-fusion protein, overrides the inhibition of phagocytosis by blocking the “don’t eat me” signal through CD47 and delivers a pro-phagocytic (“eat”) signal through engagement of Fcγ receptors on macrophages and NK cells. In this first-in-human study, TTI-621 was well tolerated and showed evidence of activity as monotherapy in a variety of hematologic malignancies, demonstrating clinical proof of principle for targeting the CD47-SIRPα axis by the dual mechanisms of TTI-621. The low incidence of anemia was consistent with prior preclinical observations that TTI-621 binds minimally to erythrocytes. Thrombocytopenia, initially identified as a dose limiting toxicity that determined MTD, has shown to be transient with no clinical sequelae. Further dose optimization currently in process is needed to assess the full potential of TTI-621 as a new cancer immunotherapy.

Word count: 148 (limit, 150)
Abstract

Purpose: TTI-621 (SIRPα-IgG1 Fc) is a novel checkpoint inhibitor that activates antitumor activity by blocking the CD47 “don’t eat me” signal. This first-in-human phase 1 study (NCT02663518) evaluated the safety and activity of TTI-621 in relapsed/refractory (R/R) hematologic malignancies.

Patients and Methods: Patients with R/R lymphoma received escalating weekly intravenous TTI-621 to determine the maximum tolerated dose (MTD). During expansion, patients with various malignancies received weekly single-agent TTI-621 at the MTD; TTI-621 was combined with rituximab in patients with B-cell non-Hodgkin lymphoma (NHL) or nivolumab in patients with Hodgkin lymphoma. The primary endpoint was the incidence/severity of adverse events (AEs). Secondary endpoints included overall response rate (ORR).

Results: Overall, 164 patients received TTI-621: 18 in escalation and 146 in expansion (rituximab combination, n=35; nivolumab combination, n=4). Based on transient grade 4 thrombocytopenia, the MTD was determined as 0.2 mg/kg; 0.1 mg/kg was evaluated in combination cohorts. AEs included infusion-related reactions, thrombocytopenia, chills, and fatigue. Thrombocytopenia (20% grade ≥3) was reversible between doses and not associated with bleeding. Transient thrombocytopenia that determined the initial MTD may not have been dose limiting. The ORR for all patients was 13%. The ORR was 29% (2/7) for diffuse large B-cell lymphoma (DLBCL) and 25% (8/32) for T-cell NHL (T-NHL) with TTI-621 monotherapy and was 21% (5/24) for DLBCL with TTI-621 plus rituximab. Further dose optimization is ongoing.

Conclusions: TTI-621 was well tolerated and demonstrated activity as monotherapy in patients with R/R B-NHL and T-NHL and combined with rituximab in patients with R/R B-NHL.
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1 NHL.

2 Word count: 249 (limit, 250)
Introduction

CD47 is a ubiquitously expressed transmembrane protein that binds signal regulatory protein alpha (SIRPα) and other ligands on myeloid cells, generating a “don’t eat me” signal that suppresses phagocytosis (1). Hematologic and solid tumors overexpress CD47, which is associated with poor prognosis (2-11), suggesting that the CD47-SIRPα axis is a widely used mechanism of immune evasion and a promising therapeutic target.

Anti-tumor activity has been shown with a humanized anti-CD47 monoclonal antibody combined with rituximab in patients with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL) (12).

TTI-621 (SIRPα-IgG1 Fc), a recombinant soluble fusion protein consisting of the CD47-binding domain of human SIRPα and the Fc region of human IgG1, binds to CD47, blocking its interaction with macrophage SIRPα and overriding the inhibition of phagocytosis. The IgG1 Fc of TTI-621 delivers a pro-phagocytic (“eat”) signal through macrophage Fcγ receptors that is important for anti-tumor activity, as CD47 blockade alone is insufficient to enable robust tumor cell phagocytosis. In preclinical studies, TTI-621 stimulated macrophage phagocytosis of cells of various hematologic and solid tumors and inhibited growth of acute myeloid leukemia (AML) and B-cell lymphoma xenografts and exhibited minimal binding to human erythrocytes (13,14), demonstrating clinical potential. This multicenter, open-label, first-in-human phase 1 study evaluated the safety, pharmacokinetics, maximum tolerated dose (MTD), pharmacodynamics, and preliminary efficacy of TTI-621 in patients with R/R hematologic malignancies or solid tumors.
Patients and Methods

Study design and participants

This open-label phase 1 study (ClinicalTrials.gov, NCT02663518) has four parts: dose escalation, initial dose expansion, focused dose expansion, and dose optimization. The dose escalation (Part 1) assessed the safety, MTD, pharmacokinetics, and pharmacodynamics of TTI-621 in patients with advanced lymphomas. The initial dose expansion (Part 2) assessed the safety and preliminary efficacy of TTI-621 as monotherapy in patients with hematologic malignancies or solid tumors and combined with rituximab in patients with CD20+ B-NHL or with nivolumab in patients with Hodgkin lymphoma (HL). The focused expansion (Part 3) recruited patients to further characterize single-agent activity of TTI-621 in cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL). Part 4 is currently ongoing to optimize the TTI-621 dose following a revised dose-limiting toxicity (DLT) criterion for thrombocytopenia (grade 4 thrombocytopenia of any duration changed to grade 4 thrombocytopenia lasting >72 hours), which was supported by the safety data collected from Parts 1 and 2.

We report Parts 1 and 2 of the study, which was conducted at 11 sites in the USA and Canada.

Adults (aged ≥18 y) had documented advanced malignancies that progressed following treatment with standard anticancer therapy, or for which there were no approved conventional therapies; Eastern Cooperative Oncology Group performance status ≤2; adequate coagulation, hepatic, and renal function; and had recovered from prior anticancer drug or radiotherapy toxicities. Patients in the dose escalation had documented, advanced lymphoma following ≥2 prior therapies, including anti-CD20 therapy for B-NHL, and adequate hematologic status (absolute neutrophil count [ANC]...
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≥1.5×10⁹/L, platelets ≥75×10⁹/L, and hemoglobin ≥100 g/L) without transfusion or growth factor support. Additional patients in the initial dose expansion had advanced small-cell lung cancer (SCLC); multiple myeloma treated with ≥3 prior therapies, including an immunomodulatory drug or proteasome inhibitor; AML; myelodysplastic syndrome (MDS); BCR/ABL1-negative myeloproliferative neoplasm (MPN); or chronic lymphocytic leukemia (CLL); indolent or aggressive B-NHL, HL, or T-cell NHL (T-NHL) treated with ≥2 prior therapies, including anti-CD20 antibodies for B-NHL; ANC ≥1×10⁹/L (not applicable for AML, MDS, or MPN); platelets ≥50×10⁹/L; and hemoglobin ≥8 g/L.

Blood transfusions were allowed in the expansion to achieve adequate ANC, platelet, and hemoglobin.

Exclusion criteria included irreversible antiplatelet/anticoagulant or investigational or anticancer therapy within 14 days (excluding hydroxyurea in myeloid malignancies); allogeneic transplant within 30 days or active graft-versus-host disease (except grade 1 skin involvement); prior anti-CD47 therapy (except prior TTI-621); history of hemolytic anemia or bleeding diathesis; prior grade 4 rituximab infusion-related reaction (rituximab combination arm); or prior or active autoimmune disease or treatment with anti-PD-1/PD-L1 or anti-CTLA4 (nivolumab combination arm).

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study was approved by local ethical review committees and institutional review boards. Patients provided written informed consent.

Procedures

The dose escalation (3+3 design) was planned to enroll patients sequentially to receive weekly intravenous TTI-621 at doses of 0.05, 0.1, 0.3, 1, 3, and 10 mg/kg for 3 weeks for the assessment of DLTs. The initial dose expansion was planned to enroll cohorts by
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1 tumor type to receive the MTD or the recommended phase 1b dose of TTI-621 weekly
2 as monotherapy. Additional cohorts were enrolled to assess weekly TTI-621 plus
3 rituximab 375 mg/m²/wk for up to eight weekly cycles or nivolumab 3 mg/kg every two
4 weeks. Inpatient dose intensification in 0.1-mg/kg increments weekly (up to a
5 maximal increase of 0.5 mg/kg) per investigator discretion based on patients' tolerability
6 of TTI-621 (prior dose associated with grade ≤2 treatment-related AEs) was allowed in
7 the dose expansion following a protocol amendment. Patients received prophylactic
8 acetaminophen and diphenhydramine for infusion-related reactions before all doses.
9 Treatment continued until disease progression, unacceptable toxicity, or other reasons.

10 A DLT was defined as any of the following treatment-emergent adverse events (AEs):
11 grade 4 thrombocytopenia of any duration (revised to grade 4 thrombocytopenia lasting
12 for at least 72 hours or a platelet count of ≤10×10⁹/L at any time in ongoing Part 4);
13 grade 3 thrombocytopenia with bleeding (except brief, controlled epistaxis, mild gum
14 bleeding, or normal menses) or requiring platelet transfusion; grade 4 anemia
15 unexplained by disease; grade 4 neutropenia lasting >5 days; febrile neutropenia (ANC
16 <1.0×10⁹/L with fever >38.5°C); grade ≥3 non-hematologic toxicity except for alopecia or
17 managed nausea; grade 3 or 4 hemorrhage; or grade 3 or 4 cytokine release syndrome
18 per National Cancer Institute Common Terminology Criteria for Adverse Events
19 (CTCAE), version 4.03. The MTD was defined as the dose level immediately below that
20 in which two or more of either three or six patients experienced a DLT during the three-
21 week observation period; at least six patients must have been treated at the putative
22 MTD with no more than one DLT. Additional details are found in the protocol.
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Safety monitoring procedures included vital signs, physical examinations, electrocardiograms, hematology and chemistry, coagulation, and urinalysis. All AEs were recorded and graded per CTCAE, version 4.03.

Clinical response was assessed at weeks 4, 8, 12, 16, and 20 (depending on tumor type) and every 12 weeks thereafter unless otherwise specified in the protocol as follows: Lugano classification (15) (with 2016 refinement (16)) for lymphoma on immunomodulatory therapy; revised International Working Group (17) for AML; International Workshop on CLL (18); International Consortium Proposal of Uniform Response Criteria for Myelodysplastic/Myeloproliferative Neoplasms (19); International Uniform Response Criteria for Multiple Myeloma (20); Clinical Endpoints and Response Criteria in Mycosis Fungoides and Sézary Syndrome (21); and adaption of Immune-Related Response Criteria for SCLC (22).

Serial serum samples for TTI-621 pharmacokinetics assessments were collected at baseline, and 1, 2, 4, 24, 72, and 168 hours after dosing in weeks 1 and 6. Additional samples were obtained from patients who received multiple TTI-621 doses or who were dose-intensified. Samples were collected within 1 week following the last dose.

Pharmacokinetic parameters included maximum serum concentration (C_{max}), area under the curve from time 0 to 168 hours post-dose (AUC_{0-168}), and terminal half-life (t_{1/2}).

CD47 receptor occupancy was measured on circulating blood cells pre-dose on day 1; on day 2 in weeks 1 and 6; pre-dose in weeks 2 and 7; and end of infusion at weeks 1 and 6. Additional samples were collected at each dose for dose-intensified patients.

Unbound CD47 was detected with the anti-CD47 antibody clone B6H12, which is competitive with SIRPαFc. CD47 expression by CD3+ T cells was measured using
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calibration beads to determine the known absolute binding capacity (ABC). Receptor occupancy was reported as $1 - (\text{ABC}_{\text{Post}}/\text{ABC}_{\text{Pre}}) \times 100$.

**Endpoints**

The primary endpoint was the incidence and severity of AEs. Secondary endpoints included TTI-621 pharmacokinetics and pharmacodynamic response. Secondary endpoints in the dose expansion also included the overall response rate (ORR).

**Statistical analysis**

The data cut-off was October 1, 2018; patients were followed for response until December 31, 2018. Safety was assessed for patients who received TTI-621. ORR and treatment duration were assessed for all patients and patients with ≥1 post-baseline assessment for each disease group. Data were summarized descriptively. Noncompartmental analysis of TTI-621 pharmacokinetic parameters was performed using Phoenix® WinNonlin® software. CD47 receptor occupancy percentage was summarized by dose level.
Results

Patients and Disposition

Between February 2, 2016, and June 28, 2018, 164 patients were enrolled (dose escalation, n=18; dose expansion, n=146). Only patients with lymphomas, including HL (n=7), diffuse large B-cell lymphoma (DLBCL, n=6), follicular lymphoma (n=4), and mantle cell lymphoma (n=1; Table 1) were included in the dose escalation. Patients in the dose expansion had a variety of malignancies, including B-NHL (n=44), T-NHL (n=41 [PTCL, n=12; CTCL, n=29]), HL (n=17), AML (n=20), multiple myeloma (n=8), MDS (n=6), SCLC (n=4), CLL (n=3), and MPN (n=3). Patients in the dose escalation and expansion had received a median of four prior systemic cancer treatments. Nine patients with HL had received prior PD-1/PD-L1 therapy. In the dose escalation and dose expansion, prior stem cell transplants were received by 56% and 33% of patients, respectively (allogeneic, n=17; autologous, n=46; both, n=5), and 28% and 45%, respectively, had received radiotherapy.

All 18 patients in the dose escalation received TTI-621 monotherapy (0.05 mg/kg, n=3; 0.1 mg/kg, n=3; 0.3 mg/kg, n=5; 0.2 mg/kg, n=7; Supplemental Figure 1). All 146 patients in the dose expansion received TTI-621, including ten cohorts who received TTI-621 monotherapy (n=107) starting at 0.2 mg/kg, one cohort with CD20+ NHL who received TTI-621 (0.1 mg/kg) combined with rituximab (n=35), and one cohort with HL who received TTI-621 (0.1 mg/kg) combined with nivolumab (n=4). At the data cut-off (October 1, 2018), 13 patients in the dose expansion were still receiving treatment (TTI-621 monotherapy, n=9; TTI-621 + rituximab, n=3; TTI-621 + nivolumab, n=1). The median duration of treatment in all patients was 43 days (interquartile range [IQR],
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22–117). Overall, 47 (29%) patients received ≥3 months of treatment; one ongoing patient has received >14 months of treatment.

**Safety and Tolerability**

Three patients in the dose escalation had DLTs. A patient with B-NHL in the 0.3-mg/kg cohort had a DLT of grade 4 thrombocytopenia on day 1 that resolved the next day following platelet transfusion. A second patient with B-NHL in the 0.3-mg/kg cohort had DLTs of grade 3 elevated alanine aminotransferase and aspartate aminotransferase on day 2 and grade 4 thrombocytopenia on day 3 that lasted for 2 and 1 day, respectively; both resolved by day 8. Based on the occurrence of these DLTs and given that the 0.1-mg/kg dose was tolerated, another cohort was opened to evaluate the intermediate dose level of 0.2 mg/kg. In the 0.2-mg/kg cohort, a patient with B-NHL had a DLT of grade 3 hypophosphatemia on day 2 that resolved the next day. The event was deemed clinically nonsignificant by the investigator. Based on the occurrence of the clinically nonsignificant DLT in seven patients (six DLT-evaluable), 0.2 mg/kg was determined as the MTD for monotherapy evaluation in the dose expansion. The dose of 0.1 mg/kg was selected for evaluation in the dose expansion combination cohorts.

Treatment-emergent AEs occurred in 160 (98%) patients (Table 2). Treatment-related AEs occurred in 131 (80%) patients; grade ≥3 treatment-related AEs occurred in 60 (37%) patients. There were no apparent differences in the AE profile between groups based on tumor type (data not shown). The most common (in ≥10% of patients) treatment-related AEs were infusion-related reactions (43%), thrombocytopenia (26%), chills (18%), fatigue (15%), anemia (13%), nausea (12%), pyrexia (10%), and diarrhea (10%). Grade ≥3 treatment-related AEs occurring in more than two patients included thrombocytopenia (20%), anemia (9%), neutropenia (9%), leukopenia (4%), and
infusion-related reactions (2%). Serious treatment-related AEs occurred in 17 (10%) patients. Five patients had fatal AEs (sepsis, cardiopulmonary arrest, respiratory failure, diabetic ketoacidosis, and pneumonia); none were treatment-related.

Treatment-related infusion reactions (eg, chills, pyrexia, and hypotension) occurred in 70 (43%) patients and were rarely grade ≥3 (n=3 [2%]). Most reactions often occurred following the first dose of TTI-621 (69/105 events; 66%). Thrombocytopenia occurred acutely (typically within 4 hours) after TTI-621 administration, followed by recovery over the following week (Figure 1A). In all patients, including those with hematologic malignancies prone to thrombocytopenia (ie, severely compromised bone marrow function and requiring transfusions), median pre-dose platelet levels remained relatively stable through 12 weeks (Figure 1B), with approximately 90% of pre-dose platelet levels of grade ≤2. A minimum platelet level of 50×10^9/L was required for TTI-621 retreatment.

Five (3%) patients had interruptions due to thrombocytopenia. Ten (6%) patients had treatment-related bleeding of any grade, and two (1%) patients (AML, n=1; MDS, n=1) had treatment-related grade 3 bleeding (epistaxis). Given the prompt recovery of acute thrombocytopenia and the absence of bleeding sequelae, monotherapy doses were intensified to 0.5 mg/kg in 15 patients in the dose expansion per investigator discretion; five patients and nine patients were intensified to 0.4 mg/kg and 0.3 mg/kg, respectively.

Median post-dose platelet levels were 90×10^9/L (IQR, 55–123) at 0.2 mg/kg and 128×10^9/L (42–189) at 0.5 mg/kg (Figure 1CD). Thrombocytopenia was not worsened at 0.5 mg/kg versus 0.2 mg/kg.

Thirty-seven (23%) patients had temporary interruptions of TTI-621 dosing due to treatment-related AEs that most frequently included infusion-related reactions (9%) and neutropenia (3%). Three (2%) patients had TTI-621 dose reductions owing to treatment...
related AEs, which were grade 3 hypophosphatemia in the first patient, grade 3 ALT and AST increase and grade 4 thrombocytopenia in the second patient, and grade 4 thrombocytopenia in the third patient. The dose reductions occurred early (ie, study weeks 2–3). These three patients remained on study for 3–9 weeks and discontinued due to progressive disease (n=2) and physician decision (n=1). There was no evidence of cumulative toxicity among patients with lengthy time on study. Discontinuation of TTI-621 due to AEs was required in ten (6%) patients (Supplemental Figure 1), six of whom had discontinuations owing to AEs deemed related or possibly related to TTI-621:

infusion-related reaction (n=2), sepsis (n=1), erythroleukemia (n=1), cellulitis (n=1), and pancytopenia (n=1). The patient with DLBCL who discontinued TTI-621 at week 38 due to erythroleukemia (related to prior chemotherapy and possibly related to study treatment) had achieved CR at week 12 before subsequently developing new lesions at week 36 and a concurrent secondary malignancy. The patient with mantle cell lymphoma who discontinued TTI-621 at week 39 due to treatment-related cellulitis had achieved CR at week 8.

Pharmacokinetics

Eighteen patients had available single-dose TTI-621 pharmacokinetic data during week 1 of the dose escalation (0.05 mg/kg, n=3; 0.1 mg/kg, n=3; 0.2 mg/kg, n=7; 0.3 mg/kg, n=5). TTI-621 exposure (C_{max} and AUC_{0−168}) increased with dose following a single infusion. Estimated t_{1/2} appeared dose-dependent between 0.1 mg/kg and 0.3 mg/kg, with mean t_{1/2} of 10–82.4 hours. The short t_{1/2} values after a single infusion were likely due to target-mediated clearance. At 0.2 mg/kg, mean±SD C_{max} was 976±267 ng/mL (n=6) and AUC_{0−168} was 40,715±7080 ng*h/mL (n=6) following the sixth infusion; estimated t_{1/2} was 100±12 hours (n=6). Mean serum concentrations of TTI-621 following six weekly infusions are summarized in Figure 2A.
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pharmacokinetic data in the dose expansion (0.2 mg/kg; n=46) were consistent with those in the dose escalation (n=6).

**CD47 Receptor Occupancy**

Samples for evaluating CD47 receptor occupancy on circulating T cells were obtained from 120 (73%) patients treated with TTI-621 at 0.1 mg/kg (combination), 0.2 mg/kg (monotherapy), or 0.3−0.5 mg/kg (monotherapy intensification). An increasing level of target engagement consistent with increased dose and systemic exposure was apparent (Figure 2B). Median post-infusion receptor occupancy among patients who received TTI-621 0.2 mg/kg was 33% at week 1 and 55% after the sixth infusion of TTI-621 (data not shown). Receptor occupancy peaked at a median of 66% among patients who received TTI-621 0.5 mg/kg.

**Efficacy**

Overall, 140 of 164 patients were evaluable for response; 24 patients were unevaluable.

Twenty-two of 164 (13%) patients had objective responses, including seven (4%) with a complete response (CR) and 15 (9%) with a partial response (PR; Table 3). Objective responses were observed for patients with B-NHL, T-NHL, and HL receiving TTI-621 as a monotherapy or in combinations. Among 31 evaluable patients with DLBCL, seven (23%) had objective responses, including two of seven (29%; CR, n=1; PR, n=1) who received TTI-621 monotherapy and five of 24 (21%; CR, n=1; PR, n=4) who received TTI-621 combined with rituximab (Figure 3). Of 10 patients with B-cell lymphoma who had objective responses, two responders to TTI-621 monotherapy had prior treatment with rituximab, and seven responders to TTI-621 combined with rituximab had prior treatment with rituximab. Among 32 evaluable patients with T-NHL, eight (25%) had objective responses (all with TTI-621 monotherapy), including one of four (25%) with
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1 Sézary syndrome, five of 19 (26%) with mycosis fungoides, and two of nine (22%) with
2 PTCL (angioimmunoblastic T-cell lymphoma; not otherwise specified). Among patients
3 with DLBCL and T-NHL, median overall times to response were 78 and 65 days,
4 respectively, and median treatment durations were 143 and 181 days (Figure 3).
5 Whereas one of 20 patients with HL achieved PR on TTI-621 monotherapy, among four
6 evaluable patients with HL who received TTI-621 combined with nivolumab, one (25%)
7 achieved CR and one (25%) achieved PR.

8 Among 20 enrolled patients with AML, most (90%) were treated with a high baseline of
9 disease and none achieved remission while receiving TTI-621. The other two patients
10 were in morphologic CR/CRi (one for each) at the time of enrollment with measurable
11 residual disease, one of whom rapidly achieved a complete molecular response (CMR)
12 that was durable throughout the study (weeks 4–36). The other patient in baseline
13 morphologic CR maintained stable levels of residual disease during a short, 8-week
14 course of study treatment.
Discussion

TTI-621 is a unique innate immune checkpoint inhibitor that triggers macrophage-mediated destruction of tumor cells by blocking the suppressive CD47 “don’t eat me” signal and delivering an activating pro-phagocytic signal through IgG1 engagement of Fcγ receptors. This dual mechanism distinguishes TTI-621 from other monoclonal antibodies targeting the CD47-SIRPα axis, which are mostly IgG4-based and likely require co-administration of a second agent to deliver a pro-phagocytic signal and achieve full activity (13,14,23). In addition, TTI-621 binds minimally to human erythrocytes, a phenomenon that has been attributed to its affinity for CD47 and the unique structure of CD47 in the erythrocyte membrane (13). This unusual property is predicted to reduce the risk of anemia in patients, diminish the likelihood of interference with transfusion testing, and decrease the CD47 antigen sink that could potentially impede TTI-621 exposure.

In this study, based on the occurrence of DLTs per protocol in two patients in the 0.3-mg/kg cohort, the MTD of TTI-621 for evaluation as monotherapy in the dose expansion was determined as 0.2 mg/kg, and 0.1 mg/kg was selected for evaluation in combination cohorts. TTI-621 was well tolerated at 0.2 mg/kg; treatment-related AEs were generally mild or moderate in severity and there were no deaths due to treatment-related AEs.

Consistent with reports of other agents targeting CD47 in hematologic malignancies and solid tumors (12,24-26), the most common AEs during treatment with TTI-621 included infusion-related reaction, thrombocytopenia, chills, fatigue, anemia, nausea, pyrexia, and diarrhea. The incidence of treatment-related anemia (any grade, 13%; grade ≥3, 9%) was lower than that reported in a phase 1 study of the humanized anti-CD47 monoclonal antibody Hu5F9-G4 combined with rituximab, in which 41% of patients with R/R NHL...
TTI-621 in Patients With R/R Hematologic Malignancies

1 had treatment-related anemia, with the majority grade 3 (12). Notably, the occurrence of
2 anemia with Hu5F9-G4 followed the use of an anemia-mitigating priming dose regimen
3 that was not necessary for administration of TTI-621. However, the incidence of grade
4 ≥3 treatment-related thrombocytopenia was higher with TTI-621 (20% vs ~5%).

5 Treatment-related thrombocytopenia during TTI-621 therapy is postulated to be an on-
6 target effect involving platelet removal by macrophages following CD47 blockade and
7 the delivery of an activating IgG1 signal. It is reversible and typically resolved within one
8 week. The recovery from thrombocytopenia starts immediately following an acute phase
9 of platelet decrease on the dosing days. It is likely that platelets sequestered in spleen,
10 which normally account for 30% of the total platelet reserve, entered into the periphery
11 as an instant compensatory response. The week-long gradual course of recovery was
12 consistent with the physiologic half-life of platelets, likely reflecting replenishing through
13 production in the bone marrow. Due to its transient nature, thrombocytopenia observed
14 on study did not result in severe bleeding (1% of patients) or dosing interruptions (1% of
15 patients). For these reasons, and because platelet levels remained relatively stable
16 throughout the study, TTI-621 monotherapy doses were intensified in 15 patients in the
17 dose expansion, up to 0.5 mg/kg. These dose intensifications did not increase the
18 incidence of thrombocytopenia and platelet levels were generally consistent with those
19 at 0.2 mg/kg, indicating that patients tolerate doses above the formally declared MTD.
20 Therefore, the initially defined MTD of 0.2 mg/kg may have underestimated the true
21 MTD. Of note, the protocol-specified DLT criterion of grade 4 thrombocytopenia of any
22 duration appears too conservative based on the transient and clinically inconsequential
23 nature of the thrombocytopenia associated with TTI-621. Thus, the study protocol DLT
24 criterion for thrombocytopenia has been revised from grade 4 of any duration to grade 4
TTI-621 in Patients With R/R Hematologic Malignancies

lasting for at least 72 hours in the ongoing dose optimization phase (Part 4) of the study (27).

Systemic exposure to TTI-621 appeared dose-dependent without a plateau at the highest dose (0.5 mg/kg) evaluated. Receptor occupancy, which was 34% at 0.2 mg/kg, increased to 66% after intrapatient dose intensification to 0.5 mg/kg. Collectively with safety and tolerability, these pharmacokinetic and pharmacodynamic data support ongoing evaluation of higher doses greater than 0.5 mg/kg. Additional clinical benefit may be achieved with further dose escalation of TTI-621 as monotherapy and further in combination with other agents.

CD47 is broadly expressed in many cancer types (1). As such, this study incorporated an empirical approach during the dose expansion to evaluate the clinical activity of TTI-621 in a variety of hematologic malignancies as a monotherapy or combined with rituximab or nivolumab. Despite the fact that most patients received a relatively low dose of 0.2 mg/kg, objective responses occurred in patients who received TTI-621 monotherapy, including eight of 40 (20%) with T-NHL. A parallel phase 1 study of TTI-621 administered by intralesional injection (NCT02890368) showed activity of TTI-621 monotherapy against skin lesions in over 90% of patients with CTCL (28), supporting the notion that TTI-621 is active as monotherapy in T-cell malignancies. TTI-621 appears to have the potential to become an effective therapy for CTCL that can be administered either locally for early stage disease or systemically to target advanced stage disease. Monotherapy activity was also observed in two of 12 (17%) patients with aggressive B-NHL, and one of 20 (5%) with HL. The limited evidence of TTI-621 activity in patients with AML was surprising given prior preclinical evidence in AML and the importance of CD47 as a prognostic marker in the disease (8,13); however, one of two
TTI-621 in Patients With R/R Hematologic Malignancies

patients with AML achieved CMR with evidence of residual disease with molecular
testing, suggesting that additional investigation with an optimized dose in the low
disease burden setting is needed.

TTI-621 (0.1 mg/kg) combined with rituximab led to objective responses in 23% of all
patients with R/R B-NHL. Although the response rate was similar with that of TTI-621
monotherapy in the same population or numerically less in sub-populations, such as
DLBCL (29% vs 21%), the limited sample size precludes any meaningful comparison
between the two groups. A phase 1 study demonstrated an objective response rate of
50% with Hu5F9-G4 combined with rituximab in patients with R/R B-NHL (12). Further
evaluation of TTI-621 upon completion of the dose optimization is warranted in this
setting. Additionally, TTI-621 as an IgG-1 based molecule may provide adequate
intrinsic activation signals that negate the need for co-administration of another IgG-
bearing antibody agent.

Overall, this phase 1 study has confirmed that blockade of the CD47-SIRPα axis with
TTI-621 is well tolerated and results in clinical responses in patients with various
hematologic malignancies, including B-NHL and T-NHL. A detailed characterization of
the transient thrombocytopenia following TTI-621 administration has enabled dose
intensification beyond the initially defined single agent MTD of 0.2 mg/kg with no obvious
safety findings and improved receptor occupancy. The activity of TTI-621 monotherapy
in this study suggests that TTI-621 has the potential to be a monotherapy, in contrast
with anti-CD47 agents incorporating less active Fc regions, which require combination
with a second agent to elicit the necessary pro-phagocytic signal. The low incidence of
anemia in this study was consistent with prior preclinical observations that TTI-621 binds
minimally to erythrocytes. Furthermore, the observed efficacious dose range of TTI-621
TTI-621 in Patients With R/R Hematologic Malignancies

1 appeared lower than an IgG4-based anti-CD47 antibody that binds erythrocytes, likely due to the more active IgG1 Fc of TTI-621 and its ability to avoid the large antigen sink on erythrocytes.

4 Having established preliminary efficacy, the next objective is to identify the recommended phase 2 dose of TTI-621 in Part 4 of this ongoing study. Once the dose is determined, the therapeutic potential of TTI-621 as monotherapy and combined with other immuno-oncology agents will be explored further in future studies.
TTI-621 in Patients With R/R Hematologic Malignancies

Acknowledgments

This study was funded by Trillium Therapeutics Inc. Medical writing support was provided by Ben Scott (Scott Medical Communications, LLC) and was funded by Trillium Therapeutics Inc.
TTI-621 in Patients With R/R Hematologic Malignancies

References

TTI-621 in Patients With R/R Hematologic Malignancies


TTI-621 in Patients With R/R Hematologic Malignancies

Table 1. Demographics and Baseline Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Dose Escalation (n=18)</th>
<th>Dose Expansion (n=146)</th>
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<tbody>
<tr>
<td>Median (range) age, years</td>
<td>44 (21–72)</td>
<td>64 (21–84)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>10 (56)</td>
<td>89 (61)</td>
</tr>
<tr>
<td>Women</td>
<td>8 (44)</td>
<td>57 (39)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>13 (72)</td>
<td>115 (79)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (11)</td>
<td>14 (10)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (6)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (6)</td>
<td>3 (2)</td>
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<td>Unknown</td>
<td>1 (6)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>6 (33)</td>
<td>41 (28)</td>
</tr>
<tr>
<td>1</td>
<td>12 (67)</td>
<td>89 (61)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>16 (11)</td>
</tr>
<tr>
<td>Malignancies, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>B-cell non-Hodgkin lymphoma</td>
<td>11 (61)</td>
<td>44 (30)</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>6 (33)</td>
<td>29&lt;sup&gt;a&lt;/sup&gt; (20)</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>4 (22)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>1 (6)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Other&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
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<td>41&lt;sup&gt;c&lt;/sup&gt; (28)</td>
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<td>Peripheral T-cell lymphoma</td>
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<td>Cutaneous T-cell lymphoma</td>
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<td>Mycosis fungoides</td>
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<td>Sézary syndrome</td>
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<td>17 (12)</td>
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<td>Non-lymphomas</td>
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<td>Myelodysplastic syndrome</td>
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<td>Multiple myeloma</td>
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</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
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</tr>
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### TTI-621 in Patients With R/R Hematologic Malignancies

<table>
<thead>
<tr>
<th>Disease status, n (%)</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsed</td>
<td>10 (56)</td>
<td>81 (55)</td>
</tr>
<tr>
<td>Refractory</td>
<td>8 (44)</td>
<td>62 (42)</td>
</tr>
<tr>
<td>Median (range) prior systemic treatments</td>
<td>4 (2−19)</td>
<td>4 (1−18)</td>
</tr>
<tr>
<td>Prior stem cell transplant, n (%)</td>
<td>10 (56)</td>
<td>48 (33)</td>
</tr>
<tr>
<td>Prior radiotherapy, n (%)</td>
<td>5 (28)</td>
<td>66 (45)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified.

*a Two patients from the dose escalation (0.05 mg/kg and 0.2 mg/kg) were re-enrolled into the rituximab combination dose expansion cohort.

*b Includes primary mediastinal large B-cell lymphoma (n=1), marginal zone lymphoma (n=1), transformed lymphoma (n=1), indolent B-cell lymphoma, not otherwise specified (n=1).

*c One patient enrolled in the rituximab combination cohort had a diagnosis change from diffuse large B-cell lymphoma to peripheral T-cell lymphoma.
Table 2. Summary of Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any treatment-emergent AE, n (%)</td>
<td>160 (98)</td>
<td>100 (61)</td>
</tr>
<tr>
<td>Patients with any treatment-related AE, n (%)</td>
<td>131 (80)</td>
<td>60 (37)</td>
</tr>
<tr>
<td>Patients with any treatment-related serious AE, n (%)</td>
<td>17 (10)</td>
<td>14 (9)</td>
</tr>
<tr>
<td>Treatment-related AEs occurring in ≥5% of patients, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>70 (43)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>43 (26)</td>
<td>33 (20)</td>
</tr>
<tr>
<td>Chills</td>
<td>30 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>22 (13)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (10)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>15 (9)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 (9)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>8 (5)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

AE, adverse event.
**Table 3. Overall Response in the Dose Escalation and Dose Expansion**

<table>
<thead>
<tr>
<th></th>
<th>Overall Response (Complete + Partial)</th>
<th>Complete Response</th>
<th>Partial Response</th>
<th>Stable Disease</th>
<th>Progressive Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>22/164 (13%)</td>
<td>7/164 (4%)</td>
<td>15/164 (9%)</td>
<td>57/164 (35%)</td>
<td>61/164 (37%)</td>
</tr>
<tr>
<td>B-cell non-Hodgkin lymphoma (monotherapy)</td>
<td>2/21 (10%)</td>
<td>1/21 (5%)</td>
<td>1/21 (5%)</td>
<td>11/21 (52%)</td>
<td>6/21 (29%)</td>
</tr>
<tr>
<td>Aggressive b</td>
<td>2/12 (17%)</td>
<td>1/12 (8%)</td>
<td>1/12 (8%)</td>
<td>4/12 (33%)</td>
<td>4/12 (33%)</td>
</tr>
<tr>
<td>Indolent</td>
<td>0/9 (0%)</td>
<td>0</td>
<td>0</td>
<td>7/9 (78%)</td>
<td>2/9 (22%)</td>
</tr>
<tr>
<td>B-cell non-Hodgkin lymphoma (rituximab combination) c</td>
<td>8/35 (23%)</td>
<td>3/35 (9%)</td>
<td>5/35 (14%)</td>
<td>13/35 (37%)</td>
<td>11/35 (31%)</td>
</tr>
<tr>
<td>Aggressive</td>
<td>6/30 (20%)</td>
<td>2/30 (7%)</td>
<td>4/30 (13%)</td>
<td>11/30 (37%)</td>
<td>11/30 (37%)</td>
</tr>
<tr>
<td>Indolent</td>
<td>2/4 (50%)</td>
<td>1/4 (25%)</td>
<td>1/4 (25%)</td>
<td>2/4 (50%)</td>
<td>0</td>
</tr>
<tr>
<td>T-cell non-Hodgkin lymphoma</td>
<td>8/40 (20%)</td>
<td>1/40 (3%)</td>
<td>7/40 (18%)</td>
<td>14/40 (35%)</td>
<td>10/40 (25%)</td>
</tr>
<tr>
<td>Cutaneous T-cell lymphoma</td>
<td>6/29 (21%)</td>
<td>1/29 (3%)</td>
<td>5/29 (17%) d</td>
<td>11/29 (38%)</td>
<td>6/29 (21%)</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma</td>
<td>2/11 (18%)</td>
<td>0</td>
<td>2/11 (18%)</td>
<td>3/11 (27%)</td>
<td>4/11 (21%)</td>
</tr>
<tr>
<td>Hodgkin lymphoma e</td>
<td>3/24 (13%)</td>
<td>1/24 (4%)</td>
<td>2/24 (8%)</td>
<td>12/24 (50%)</td>
<td>7/24 (29%)</td>
</tr>
<tr>
<td>Acute myeloid leukemia f</td>
<td>1/20 (5%) i</td>
<td>1/20 (5%) i</td>
<td>0</td>
<td>1/20 (5%) i</td>
<td>15/20 (75%)</td>
</tr>
<tr>
<td>Other g</td>
<td>0/24 (0%)</td>
<td>0</td>
<td>0</td>
<td>6/24 (25%)</td>
<td>12/24 (50%)</td>
</tr>
</tbody>
</table>

a Denominators in the table include patients who were unevaluable for response.

b Includes one complete response and one partial response in seven patients with diffuse large B-cell lymphoma.

c Includes eight responses, including three complete responses (diffuse large B-cell lymphoma, one of 26 patients; mantle cell lymphoma, one of three patients; follicular lymphoma, one of three patients) and five partial responses (diffuse large B-cell lymphoma, four of 26 patients; follicular lymphoma, one of three patients). One patient with peripheral T-cell lymphoma was not assessed for response but was included in the denominator.

d Includes one partial response assessed per Lugano criteria in the absence of skin assessment.

e Hodgkin lymphoma includes 20 patients who received TTI-621 monotherapy (one partial response) and four patients who received

---

TTI-621 in Patients With R/R Hematologic Malignancies

Table 3. Overall Response in the Dose Escalation and Dose Expansion:

<table>
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<td>6/21 (29%)</td>
</tr>
<tr>
<td>Aggressive b</td>
<td>2/12 (17%)</td>
<td>1/12 (8%)</td>
<td>1/12 (8%)</td>
<td>4/12 (33%)</td>
<td>4/12 (33%)</td>
</tr>
<tr>
<td>Indolent</td>
<td>0/9 (0%)</td>
<td>0</td>
<td>0</td>
<td>7/9 (78%)</td>
<td>2/9 (22%)</td>
</tr>
<tr>
<td>B-cell non-Hodgkin lymphoma (rituximab combination) c</td>
<td>8/35 (23%)</td>
<td>3/35 (9%)</td>
<td>5/35 (14%)</td>
<td>13/35 (37%)</td>
<td>11/35 (31%)</td>
</tr>
<tr>
<td>Aggressive</td>
<td>6/30 (20%)</td>
<td>2/30 (7%)</td>
<td>4/30 (13%)</td>
<td>11/30 (37%)</td>
<td>11/30 (37%)</td>
</tr>
<tr>
<td>Indolent</td>
<td>2/4 (50%)</td>
<td>1/4 (25%)</td>
<td>1/4 (25%)</td>
<td>2/4 (50%)</td>
<td>0</td>
</tr>
<tr>
<td>T-cell non-Hodgkin lymphoma</td>
<td>8/40 (20%)</td>
<td>1/40 (3%)</td>
<td>7/40 (18%)</td>
<td>14/40 (35%)</td>
<td>10/40 (25%)</td>
</tr>
<tr>
<td>Cutaneous T-cell lymphoma</td>
<td>6/29 (21%)</td>
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<td>11/29 (38%)</td>
<td>6/29 (21%)</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma</td>
<td>2/11 (18%)</td>
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<td>2/11 (18%)</td>
<td>3/11 (27%)</td>
<td>4/11 (21%)</td>
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<tr>
<td>Hodgkin lymphoma e</td>
<td>3/24 (13%)</td>
<td>1/24 (4%)</td>
<td>2/24 (8%)</td>
<td>12/24 (50%)</td>
<td>7/24 (29%)</td>
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<tr>
<td>Acute myeloid leukemia f</td>
<td>1/20 (5%) i</td>
<td>1/20 (5%) i</td>
<td>0</td>
<td>1/20 (5%) i</td>
<td>15/20 (75%)</td>
</tr>
<tr>
<td>Other g</td>
<td>0/24 (0%)</td>
<td>0</td>
<td>0</td>
<td>6/24 (25%)</td>
<td>12/24 (50%)</td>
</tr>
</tbody>
</table>

a Denominators in the table include patients who were unevaluable for response.

b Includes one complete response and one partial response in seven patients with diffuse large B-cell lymphoma.

c Includes eight responses, including three complete responses (diffuse large B-cell lymphoma, one of 26 patients; mantle cell lymphoma, one of three patients; follicular lymphoma, one of three patients) and five partial responses (diffuse large B-cell lymphoma, four of 26 patients; follicular lymphoma, one of three patients). One patient with peripheral T-cell lymphoma was not assessed for response but was included in the denominator.

d Includes one partial response assessed per Lugano criteria in the absence of skin assessment.

e Hodgkin lymphoma includes 20 patients who received TTI-621 monotherapy (one partial response) and four patients who received...
TTI-621 combined with nivolumab (one complete response; one partial response).

\(^1\)Includes two AML patients who were in morphological CR or CRi (one patient each) at the time of enrollment but cytogenetically relapsed with measurable baseline minimal residue disease. One patient achieved complete molecular remission on study, and the other had stable disease (maintaining in morphologic CRi with MRD per FISH). The remaining 18 patients were treated with higher baseline disease burden, and none of them have obtained remission.

\(^9\)Other includes small cell lung cancer (n=4), multiple myeloma (n=8), myelodysplastic syndrome (n=6), chronic lymphocytic leukemia (n=3), and myeloproliferative neoplasm (n=3).
TTI-621 in Patients With R/R Hematologic Malignancies

Figure Legends

**Figure 1.** Platelet Response. A, week 1 platelet response in all patients at all doses. B, median (IQR) pre-dose platelet concentration. C, acute post-dose platelet changes in dose intensified patients. D, acute post-dose platelet changes in dose-intensified patients. Median (IQR), min.

**Figure 2.** Pharmacokinetics and pharmacodynamic response. A, mean change in systemic exposure of TTI-621 by dose level within 168 hours following six weekly infusions of TTI-621 (n=13) during the dose escalation. B, Post-infusion CD47 receptor occupancy on circulating CD3+ T cells by dose level (n=120). Post-infusion values were taken from different infusions. *Data outlier.

**Figure 3.** Best response in response evaluable patients with DLBCL (A) and T-cell lymphoma (B). DLBCL, diffuse large B-cell lymphoma; CR, complete response; MF, mycosis fungoides; PD, progressive disease; PR, partial response; PTCL, peripheral T-cell lymphoma; SD, stable disease; SS, Sézary Syndrome. Red asterisks indicate the beginning of objective response. Arrows indicate treatment ongoing.
Figure 1

A

Platelets (× 10^9/L)

Day

n

0 153

2 156

4 152

6 145

8 183

B

Platelets (× 10^9/L)

Week

n

1 164

3 183

5 164

7 181

9 157

11 161

13 160

15 175

17 158

19 181

21 173

23 167

C

Platelets (× 10^9/L)

Dose (Visit) 0.2 mg/kg (Wk 1) 0.5 mg/kg (Wks 5–30)

Pre-Post Dose Pre Post Pre Post

n 15 15 15 14

Gr 4, n (%)

n

0 153

3 145

6 127

9 116

12 102

15 93

18 86

21 68

24 66

27 59

30 61

33 51

D

Platelets (× 10^9/L)

Dose (Visit) 0.2 mg/kg (Wk 1) 0.5 mg/kg (Wks 5–30)

Pre-Post Dose Pre Post Pre Post

n 15 15 15 14

IQR

(145, 266) (55, 123) (123, 246) (42, 189)
Figure 2

A

Mean Concentration (ng/mL) vs Time (h)

B

CD47 Receptor Occupancy on Circulating CD3+ T Cells (%)

Median (IQR)

0.1 mg/kg: 30.3 (18.5–38.0)
0.2 mg/kg: 34.4 (23.4–47.0)
0.3 mg/kg: 58.3 (35.6–65.4)
0.4 mg/kg: 62.5 (45.6–73.7)
0.5 mg/kg: 66.1 (40.1–73.1)

n: 26, 90, 22, 15, 13
## Figure 3

### A

**Best Response in Patients with DLBCL**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Response, n (%)</th>
<th>Median (Range) Time to Response, d</th>
<th>Median (Range) Treatment Duration, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTI-621</td>
<td>7</td>
<td>CR: 1 (14) PR: 1 (14) Total: 2 (29)</td>
<td>106 (78–133)</td>
<td>139 (134–143)</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>CR: 2 (6) PR: 5 (16) Total: 7 (23)</td>
<td>78 (21–133)</td>
<td>143 (127–469)</td>
</tr>
</tbody>
</table>

### B

**Best Response in Patients with T-Cell Lymphoma**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Response, n (%)</th>
<th>Median (Range) Time to Response, d</th>
<th>Median (Range) Treatment Duration, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>MF</td>
<td>19</td>
<td>CR: 0 PR: 5 (26) Total: 5 (26)</td>
<td>50 (23–218)</td>
<td>135 (41–338)</td>
</tr>
<tr>
<td>SS</td>
<td>4</td>
<td>CR: 1 (25) PR: 0 Total: 1 (25)</td>
<td>303 (303–303)</td>
<td>373 (373–373)</td>
</tr>
<tr>
<td>PTCL</td>
<td>9</td>
<td>CR: 0 PR: 2 (22) Total: 2 (22)</td>
<td>50 (20–79)</td>
<td>302 (127–477)</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>CR: 1 (3) PR: 7 (22) Total: 8 (25)</td>
<td>65 (20–303)</td>
<td>181 (41–477)</td>
</tr>
</tbody>
</table>
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