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

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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 I 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 (B-NHL) or with nivolumab in patients with Hodgkin lymphoma. The primary endpoint was the incidence/severity of adverse events (AEs). Secondary endpoint included overall response rate (ORR).

Results: Overall, 164 patients received TTI-621: 18 in escalation and 146 in expansion (rituximab combination, $n = 35$ and nivolumab combination, $n = 4$). On the basis of 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.

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. Antitumor activity has been shown with a humanized anti-CD47 mAb combined with rituximab in patients with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL; ref. 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 prophagocytic ("eat") signal through macrophage Fcγ receptors that is important for antitumor 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 I study evaluated the safety, pharmacokinetics, 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 I study (ClinicalTrials.gov, NCT02663518) had four parts: dose escalation, initial dose expansion, focused dose

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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 prophagocytic ("eat") signal through engagement of Fcγ receptors on macrophages and natural killer 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–signal regulatory protein alpha (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, was 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.

expansion, and dose optimization. The dose-escalation group (part 1) assessed the safety, MTD, pharmacokinetics, and pharmacodynamics of TTI-621 in patients with advanced lymphomas. The initial dose-expansion group (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. 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 United States and Canada.

Adults (aged ≥18 years) recruited in the study 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 group had documented advanced lymphoma following ≥2 prior therapies, including anti-CD20 therapy for B-NHL, and adequate hematologic status [absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelets ≥75×10^9/L, and hemoglobin ≥ 100 g/L] without transfusion or growth factor support. Additional patients in the initial dose-expansion group 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); chronic lymphocytic leukemia (CLL); indolent or aggressive B-NHL, Hodgkin lymphoma, or T-cell NHL (T-NHL) treated with ≥2 prior therapies, including anti-CD20 antibodies for B-NHL; ANC ≥ 1×10^9/L (not applicable for AML, MDS, or MPN); platelets ≥ 50×10^9/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 group (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 group was planned to enroll cohorts by tumor type to receive the MTD or the recommended phase Ib dose of TTI-621 weekly as monotherapy. Additional cohorts were enrolled to assess weekly TTI-621 plus rituximab 375 mg/m^2/week for up to eight weekly cycles or nivolumab 3 mg/kg every 2 weeks. Intrapatient dose intensification in 0.1-mg/kg increments weekly (up to a maximal increase of 0.5 mg/kg) per investigator discretion based on patients' tolerability of TTI-621 [prior dose associated with grade ≤2 treatment-related adverse events (AEs)] was allowed in the dose-expansion group following a protocol amendment. Patients received prophylactic acetaminophen and diphenhydramine for infusion-related reactions before all doses. Treatment continued until disease progression, unacceptable toxicity, or other reasons.

A DLT was defined as any of the following treatment-emergent AEs: grade 4 thrombocytopenia of any duration (revised to grade 4 thrombocytopenia lasting for at least 72 hours or a platelet count of ≤10×10^9/L at any time in ongoing part 4); grade 3 thrombocytopenia with bleeding (except brief, controlled epistaxis, mild gum bleeding, or normal menses) or requiring platelet transfusion; grade 4 anemia unexplained by disease; grade 4 neutropenia lasting >5 days; febrile neutropenia (ANC < 1.0×10^9/L with fever >38.5°C); grade ≥3 nonhematologic toxicity, except for alopecia or managed nausea; grade 3 or 4 hemorrhage; or grade 3 or 4 cytokine release syndrome per NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. The MTD was defined as the dose level immediately below that in which two or more of either three or six patients experienced a DLT during the 3-week observation period; at least six patients must have been treated at the putative MTD with no more than one DLT. Additional details are found in the protocol.

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 (with 2016 refinement; refs. 15, 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. Pharmacokinetics parameters included maximum serum concentration (C_{max}), AUC from time 0 to 168 hours postdose (AUC_{0-168}), and terminal half-life ($t_{1/2}$).

CD47 receptor occupancy was measured on circulating blood cells predose on day 1, on day 2 in weeks 1 and 6, predose 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 by using calibration beads to determine the known absolute binding capacity (ABC). Receptor occupancy was reported as $1 - (ABC_{Post}/ABC_{Pre}) \times 100$.

Endpoints

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

Statistical analysis

The data cutoff 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 postbaseline assessment for each disease group. Data were summarized descriptively. Noncompartmental analysis of TTI-621 pharmacokinetics 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, $n = 18$ and dose-expansion group, $n = 146$). Only patients with lymphomas, including Hodgkin lymphoma ($n = 7$), 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 group. Patients in the dose-expansion group had a variety of malignancies, including B-NHL ($n = 44$), T-NHL [$n = 41$ (PTCL, $n = 12$ and CTCL, $n = 29$)], Hodgkin lymphoma ($n = 17$), 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 groups had received a median of four prior systemic cancer treatments. Nine patients with Hodgkin lymphoma had received prior PD-1/PD-L1 therapy. In the dose-escalation and dose-expansion groups, prior stem cell transplants were received by 56% and 33% of patients, respectively (allogeneic, $n = 17$; autologous, $n = 46$; and both, $n = 5$), and 28% and 45%, respectively, had received radiotherapy.

All 18 patients in the dose-escalation group received TTI-621 monotherapy (0.05 mg/kg, $n = 3$; 0.1 mg/kg, $n = 3$; 0.3 mg/kg, $n = 5$; and 0.2 mg/kg, $n = 7$; Supplementary Fig. S1). All 146 patients in the dose-expansion cohort received TTI-621, including 10 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 Hodgkin lymphoma who received TTI-621 (0.1 mg/kg) combined with nivolumab ($n = 4$). At the data cutoff (October 1, 2018), 13 patients in the dose-expansion group were still receiving treatment (TTI-621 monotherapy, $n = 9$; TTI-621 + rituximab, $n = 3$; and TTI-621 + nivolumab, $n = 1$). The median duration of treatment in all patients was 43 days [interquartile range (IQR), 22–117]. Overall, 47 (29%) patients received ≥3 months of treatment; one ongoing patient has received >14 months of treatment.

Table 1. Demographics and baseline disease characteristics.

	Dose escalation ($n = 18$)	Dose expansion ($n = 146$)
Median (range) age, years	44 (21–72)	64 (21–84)
Sex, *n* (%)		
Men	10 (56)	89 (61)
Women	8 (44)	57 (39)
Race, *n* (%)		
White	13 (72)	115 (79)
Black	2 (11)	14 (10)
Asian	1 (6)	11 (8)
Other	1 (6)	3 (2)
Unknown	1 (6)	3 (2)
ECOG performance status, n (%)		
0	6 (33)	41 (28)
1	12 (67)	89 (61)
2	0	16 (11)
Malignancies, *n* (%)		
B-NHL	11 (61)	44 (30)
DLBCL	6 (33)	29[a] (20)
Follicular lymphoma	4 (22)	7 (5)
Mantle cell lymphoma	1 (6)	4 (3)
Other[b]	0	4 (3)
T-cell NHL	0	41[c] (28)
PTCL	0	12 (8)
CTCL		
Mycosis fungoides	0	24 (16)
Sézary syndrome	0	5 (3)
Hodgkin lymphoma	7 (39)	17 (12)
Nonlymphomas	0	44 (30)
AML	0	20 (14)
Myelodysplastic syndrome	0	6 (4)
Multiple myeloma	0	8 (5)
CLL	0	3 (2)
MPN	0	3 (2)
SCLC	0	4 (3)
Disease status, *n* (%)		
Relapsed	10 (56)	81 (55)
Refractory	8 (44)	62 (42)
Median (range) prior systemic treatments	4 (2–19)	4 (1–18)
Prior stem cell transplant, *n* (%)	10 (56)	48 (33)
Prior radiotherapy, *n* (%)	5 (28)	66 (45)

Abbreviations: ECOG, Eastern Cooperative Oncology Group.
[a]Two patients from the dose-escalation cohort (0.05 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 DLBCL to PTCL.

Safety and tolerability

Three patients in the dose-escalation cohort 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 (ALT) and aspartate aminotransferase (AST) on day 2 and grade 4 thrombocytopenia on day 3 that lasted for 2 days and 1 day, respectively; both resolved by day 8. On the basis of 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. On the basis of 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 group. 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 (e.g., 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 (**Fig. 1A**). In all patients, including those with hematologic malignancies prone to thrombocytopenia (i.e., severely compromised bone marrow function and requiring transfusions), median predose platelet levels remained relatively stable through 12 weeks (**Fig. 1B**), with approximately 90% of predose 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, $n = 1$ and 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 group per investigator discretion; five and nine patients were intensified to 0.4 and 0.3 mg/kg, respectively. Median postdose platelet levels were 90×10^9/L (IQR, 55–123) at 0.2 mg/kg and 128×10^9/L (IQR, 42–189) at 0.5 mg/kg (**Fig. 1C** and **D**). Thrombocytopenia was not worsened at 0.5 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 (i.e., study weeks 2–3). These three patients remained on study for 3–9 weeks and discontinued because of 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 because of AEs was required in 10 (6%) patients (Supplementary Fig. S1), 6 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 because of erythroleukemia (related to prior chemotherapy and possibly related to study treatment), had achieved complete response (CR) at week 12 before subsequently developing new lesions at week 36 and a concurrent secondary malignancy. The patient with mantle cell lymphoma who

Table 2. Summary of AEs.

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

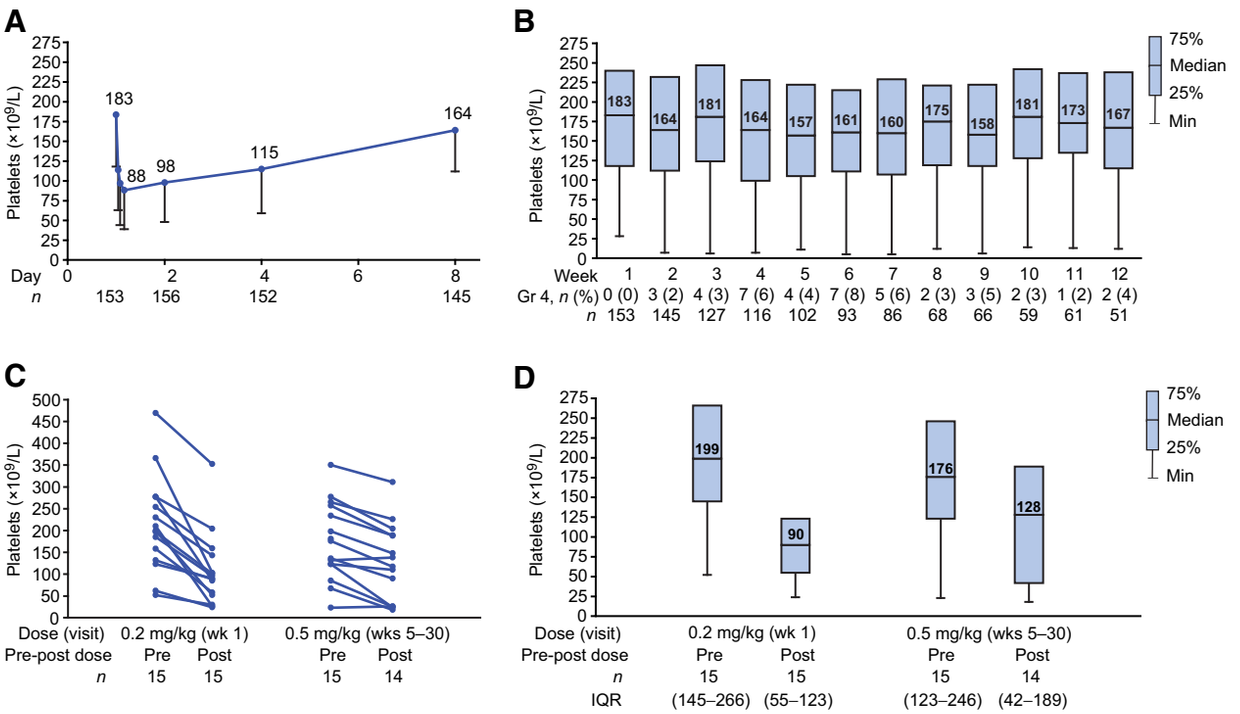

Figure 1.

Platelet response. **A,** Week 1 platelet response in all patients at all doses. **B,** Median (IQR) predose platelet concentration. **C,** Acute postdose platelet changes in dose-intensified patients. **D,** Acute postdose platelet changes in dose-intensified patients. Median (IQR), min. Gr, grade; wk, week.

discontinued TTI-621 at week 39 because of treatment-related cellulitis, had achieved CR at week 8.

Pharmacokinetics

Eighteen patients had available single-dose TTI-621 pharmacokinetics data during week 1 of the dose escalation (0.05 mg/kg, $n = 3$; 0.1 mg/kg, $n = 3$; 0.2 mg/kg, $n = 7$; and 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 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 **Fig. 2A**. Preliminary multiple dose pharmacokinetics data in the dose-expansion group (0.2 mg/kg; $n = 46$) were consistent with those in the dose-escalation cohort ($n = 6$).

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 (combination), 0.2 (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 (**Fig. 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 CR and 15 (9%) with a partial response (PR; **Table 3**). Objective responses were observed for patients with B-NHL, T-NHL, and Hodgkin lymphoma 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, $n = 1$ and PR, $n = 1$) patients who received TTI-621 monotherapy and five of 24 (21%; CR, $n = 1$ and PR, $n = 4$) patients who received TTI-621 combined with rituximab (**Fig. 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%) patients had objective responses (all with TTI-621 monotherapy), including one of four (25%) with Sézary syndrome, five of 19 (26%) with mycosis fungoides, and two of nine (22%) with PTCL (angioimmunoblastic T-cell lymphoma; not otherwise specified). Among patients with DLBCL and T-NHL, median overall times to response were 78 and 65 days, respectively, and median treatment durations were 143 and 181 days (**Fig. 3**). Whereas one of 20 patients with Hodgkin lymphoma achieved PR on TTI-621 monotherapy, among four evaluable patients with Hodgkin lymphoma who received TTI-621 combined with nivolumab, one (25%) patient achieved CR and one (25%) patient achieved PR.

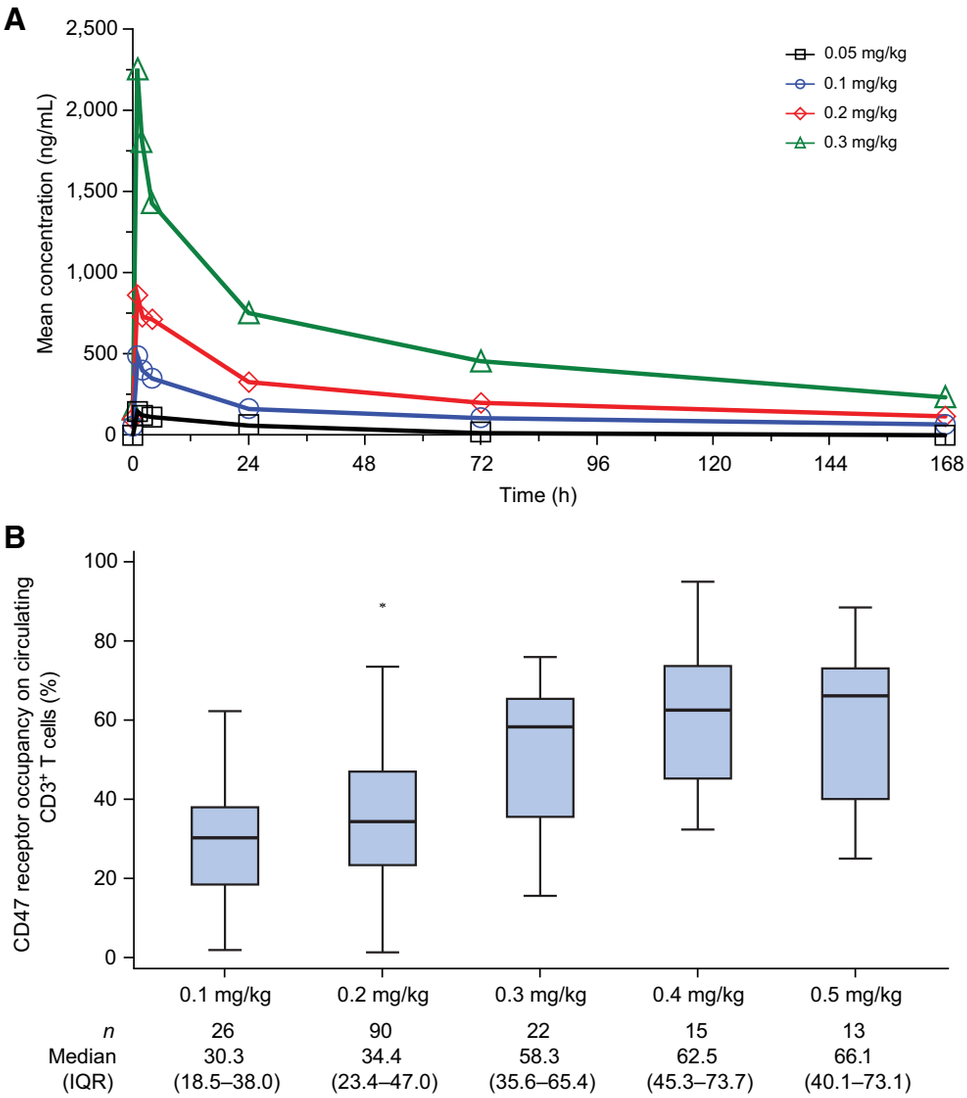

Figure 2.

Pharmacokinetics and pharmacodynamics 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,** Postinfusion CD47 receptor occupancy on circulating $CD3^+$ T cells by dose level ($n = 120$). Postinfusion values were taken from different infusions. *, Data outlier.

Among 20 enrolled patients with AML, most (90%) were treated with a high baseline of disease and none achieved remission while receiving TTI-621. The other two patients were in morphologic CR/complete remission with incomplete hematologic recovery (CRi) (one for each) at the time of enrollment with measurable residual disease, one of whom rapidly achieved a complete molecular response (CMR) that was durable throughout the study (weeks 4–36). The other patient in baseline morphologic CR maintained stable levels of residual disease during a short, 8-week 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 prophagocytic signal through IgG1 engagement of Fcγ receptors. This dual mechanism distinguishes TTI-621 from other mAbs targeting the CD47–SIRPα axis, which are mostly IgG4-based and likely require coadministration of a second agent to deliver a prophagocytic 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 cohort was determined as 0.2 mg/kg, and 0.1 mg/kg was selected for evaluation in combination

Table 3. Overall response in the dose-escalation and dose-expansion cohorts[a].

	Overall response (complete + partial)	CR	PR	Stable disease	Progressive disease
All patients	22/164 (13%)	7/164 (4%)	15/164 (9%)	57/164 (35%)	61/164 (37%)
B-NHL (monotherapy)	2/21 (10%)	1/21 (5%)	1/21 (5%)	11/21 (52%)	6/21 (29%)
Aggressive[b]	2/12 (17%)	1/12 (8%)	1/12 (8%)	4/12 (33%)	4/12 (33%)
Indolent	0/9 (0%)	0	0	7/9 (78%)	2/9 (22%)
B-NHL (rituximab combination)[c]	8/35 (23%)	3/35 (9%)	5/35 (14%)	13/35 (37%)	11/35 (31%)
Aggressive	6/30 (20%)	2/30 (7%)	4/30 (13%)	11/30 (37)	11/30 (37%)
Indolent	2/4 (50%)	1/4 (25%)	1/4 (25%)	2/4 (50%)	0
T-NHL	8/40 (20%)	1/40 (3%)	7/40 (18%)	14/40 (35%)	10/40 (25%)
CTCL	6/29 (21%)	1/29 (3%)	5/29 (17%)[d]	11/29 (38%)	6/29 (21%)
PTCL	2/11 (18%)	0	2/11 (18%)	3/11 (27%)	4/11 (36%)
Hodgkin lymphoma[e]	3/24 (13%)	1/24 (4%)	2/24 (8%)	12/24 (50%)	7/24 (29%)
AML[f]	1/20 (5%)[f]	1/20 (5%)[f]	0	1/20 (5%)[f]	15/20 (75%)
Other[g]	0/24 (0%)	0	0	6/24 (25%)	12/24 (50%)

[a]Denominators in the table include patients who were unevaluable for response.
[b]Includes one CR and one PR in seven patients with DLBCL.
[c]Includes eight responses, including three CRs (DLBCL, one of 26 patients; mantle cell lymphoma, one of three patients; and follicular lymphoma, one of three patients) and five PRs (DLBCL, four of 26 patients and follicular lymphoma, one of three patients). One patient with PTCL was not assessed for response but was included in the denominator.
[d]Includes one PR assessed per Lugano criteria in the absence of skin assessment.
[e]Hodgkin lymphoma includes 20 patients who received TTI-621 monotherapy (one PR) and four patients who received TTI-621 combined with nivolumab (one CR and one PR).
[f]Includes two patients with AML who were in morphologic CR or CRi (one patient each) at the time of enrollment, but cytogenetically relapsed with measurable baseline minimal residual disease. One patient achieved complete molecular remission on study, and the other had stable disease (maintaining in morphologic CRi with minimum residual disease per FISH). The remaining 18 patients were treated with higher baseline disease burden, and none of them have obtained remission.
[g]Other includes SCLC ($n = 4$), multiple myeloma ($n = 8$), myelodysplastic syndrome ($n = 6$), CLL ($n = 3$), and MPN ($n = 3$).

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 because of 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% and grade ≥3, 9%) was lower than that reported in a phase I study of the humanized anti-CD47 mAb, Hu5F9-G4, combined with rituximab, in which 41% of patients with R/R NHL had treatment-related anemia, the majority with grade 3 (12). Notably, the occurrence of anemia with Hu5F9-G4 followed the use of an anemia-mitigating priming dose regimen that was not necessary for administration of TTI-621. However, the incidence of grade ≥3 treatment-related thrombocytopenia was higher with TTI-621 (20% vs. ∼5%).

Treatment-related thrombocytopenia during TTI-621 therapy was postulated to be an on-target effect involving platelet removal by macrophages following CD47 blockade and the delivery of an activating IgG1 signal. It was reversible and typically resolved within 1 week. The recovery from thrombocytopenia started immediately following an acute phase of platelet decrease on the dosing days. It is likely that platelets sequestered in spleen, which normally accounts for 30% of the total platelet reserve, and entered into the periphery as an instant compensatory response. The week-long gradual course of recovery was consistent with the physiologic half-life of platelets, likely reflecting replenishing through production in the bone marrow. Because of its transient nature, thrombocytopenia observed on study did not result in severe bleeding (1% of patients) or dosing interruptions (1% of patients). For these reasons, and because platelet levels remained relatively stable throughout the study, TTI-621 monotherapy doses were intensified in 15 patients in the dose-expansion group, up to 0.5 mg/kg. These dose intensifications did not increase the incidence of thrombocytopenia and platelet levels were generally consistent with those at 0.2 mg/kg, indicating that patients tolerated doses above the formally declared MTD. Therefore, the initially defined MTD of 0.2 mg/kg may have underestimated the true MTD. Of note, the protocol-specified DLT criterion of grade 4 thrombocytopenia of any duration appears too conservative based on the transient and clinically inconsequential nature of the thrombocytopenia associated with TTI-621. Thus, the study protocol DLT criterion for thrombocytopenia has been revised from grade 4 of any duration to grade 4 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 pharmacokinetics and pharmacodynamics 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%) patients with T-NHL. A parallel phase I study of TTI-621 administered by intralesional injection (NCT02890368) showed activity of TTI-621 monotherapy against skin lesions in more than 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

A

Best response in patients with DLBCL

	n	Response, *n* (%)			Median (range) time to response, d	Median (range) treatment duration, d
		CR	PR	Total		
TTI-621	7	1 (14)	1 (14)	2 (29)	106 (78–133)	139 (134–143)
TTI-621 + R	24	1 (4)	4 (17)	5 (21)	77 (21–78)	175 (127–469)
Total	31	2 (6)	5 (16)	7 (23)	78 (21–133)	143 (127–469)

B

Best response in patients with T-cell lymphoma

	n	Response, *n* (%)			Median (range) time to response, d	Median (range) treatment duration, d
		CR	PR	Total		
MF	19	0	5 (26)	5 (26)	50 (23–218)	135 (41–338)
SS	4	1 (25)	0	1 (25)	303 (303–303)	373 (373–373)
PTCL	9	0	2 (22)	2 (22)	50 (20–79)	302 (127–477)
Total	32	1 (3)	7 (22)	8 (25)	65 (20–303)	181 (41–477)

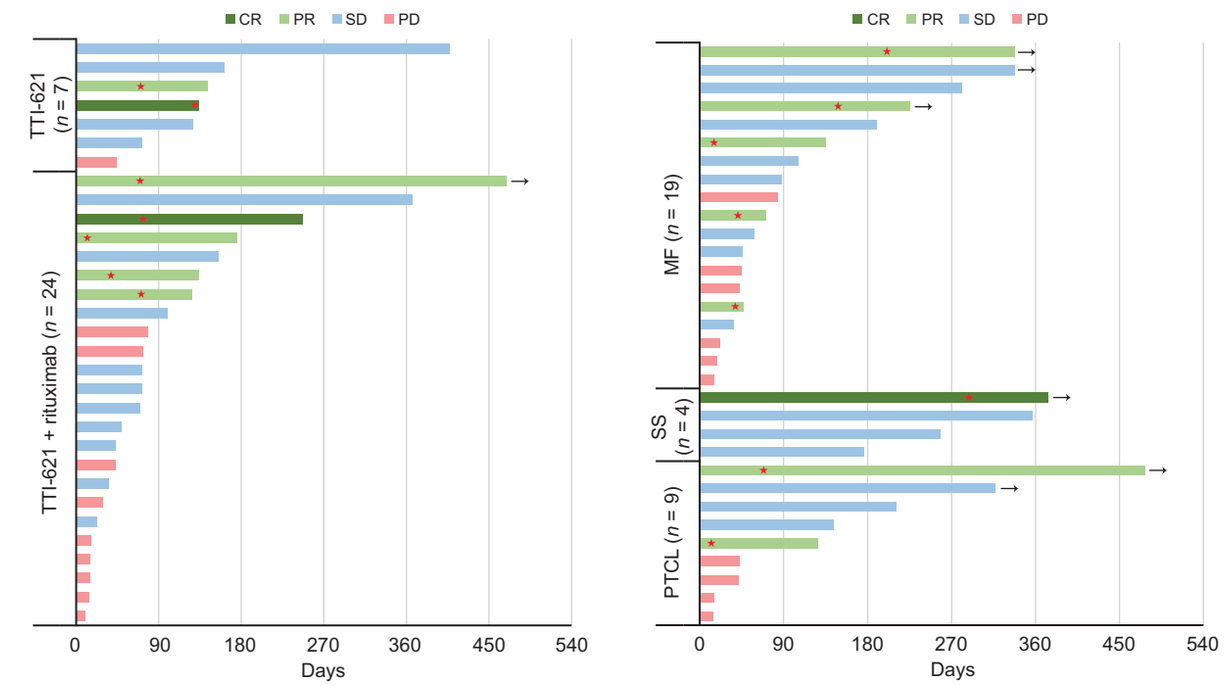

Figure 3.

Best response in response-evaluable patients with DLBCL (**A**) and T-cell lymphoma (**B**). Red asterisks indicate the beginning of objective response. Arrows indicate treatment ongoing. MF, mycosis fungoides; PD, progressive disease; SD, stable disease; SS, Sézary syndrome.

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%) patients with Hodgkin lymphoma. 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 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 subpopulations, such as DLBCL (29% vs. 21%), the limited sample size precludes any meaningful comparison between the two groups. A phase I 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. In addition, TTI-621 as an IgG1-based molecule may provide adequate intrinsic activation signals that negate the need for coadministration of another IgG-bearing antibody agent.

Overall, this phase I 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 used as a monotherapy, in contrast with anti-CD47 agents incorporating less active Fc regions, which require combination with a second agent to elicit the necessary prophagocytic 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 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.

Having established preliminary efficacy, the next objective is to identify the recommended phase II 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.

Authors' Disclosures

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