CLINICAL PROTOCOL TTI-621-01

A Phase 1a/1b Dose Escalation and Expansion Trial of TTI-621, a Novel Biologic Targeting CD47, in Subjects with Relapsed or Refractory Hematologic Malignancies and Selected Solid Tumors

Investigational Product	TTI-621 (SIRPα-IgG1 Fc)
Protocol Number	TTI-621-01
Development Phase	1a/1b
CCI	[redacted]

PPD

[redacted]

Confidentiality Statement

SYNOPSIS

TITLE:

A Phase 1a/1b Dose Escalation and Expansion Trial of TTI-621, a Novel Biologic Targeting CD47, in Subjects with Relapsed or Refractory Hematologic Malignancies and Selected Solid Tumors

PROTOCOL NUMBER: TTI-621-01

PHASE OF DEVELOPMENT: 1a/1b

INVESTIGATORS AND STUDY CENTERS: This is a multicenter trial.

OBJECTIVES:

Phase 1a Escalation

The primary objective of the escalation phase of the study is to characterize the safety profile and dose-limiting toxicities (DLT) of TTI-621 in order to identify the maximum tolerated dose (MTD) in subjects with advanced relapsed or refractory lymphomas.

Secondary objectives include characterization of the pharmacokinetics (PK), pharmacodynamics (PD), and development of antidrug antibodies (ADA).

Phase 1b Expansion (Part 2 and 3)

The primary objective of the expansion phase of the study is to further characterize the safety of TTI-621 in an expanded number of primary hematologic malignancies and selected solid tumors and to evaluate the safety of individual subject TTI-621 dose intensification.

Secondary objectives include further characterization of the PK, PD, and development of ADA; and to gain preliminary evidence of the anti-tumor activity of TTI-621 in subjects with a variety of hematologic malignancies and selected solid tumors. In addition, the safety of TTI-621 will be evaluated in combination with other anti-cancer agents.

Phase 1b Dose Optimization (Part 4)

The primary objective of the dose optimization phase is to further evaluate the safety and tolerability of TTI-621 at dose levels higher than the initially recommended phase 1b dose of 0.2 mg/kg (as determined during phase 1a dose escalation) and the MTD and/or recommended phase 2 dose will be re-assessed per revised DLT criteria following a 3+3 dose escalation schema. The DLT criteria are revised based on the totality of safety data collected thus far from the phase 1a and 1b dose expansion phase of the study. The starting dose for this further dose evaluation will be the highest dose of TTI-621 evaluated (0.5 mg/kg) during phase 1b dose expansion following dose intensification regimens permissible per protocol (Part 3).

Secondary objectives include characterization of the PK, PD, immunogenicity, and preliminary evidence of antitumor activity of TTI-621 in patients with relapsed and/or refractory CTCL at higher dose levels of TTI-621.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

TTI-621 (SIRPα-IgG1 Fc) is a soluble recombinant fusion protein created by directly linking the sequences encoding the N-terminal CD47 binding domain of human signal regulatory protein alpha (SIRPα) with the Fc domain of human immunoglobulin (IgG1). TTI-621 acts by binding human CD47 and preventing it from delivering an inhibitory "do not eat" (antiphagocytic) signal to macrophages.

TTI-621 drug product is formulated in 10 mM sodium phosphate and 150 mM sodium chloride at a pH of 7.4, supplied in single-use vials containing 5.0 mL of sterile preservative-free liquid at a concentration of 10 mg/mL.

The required dose of TTI-621 is to be diluted in 250 mL of 0.9% sodium chloride for injection USP and administered IV over 60 minutes at assigned dose levels as determined by sequential cohort assignment.

STUDY DESIGN AND METHODOLOGY:

This is a multicenter, open-label, phase 1a/1b trial of TTI-621 in subjects with relapsed or refractory hematologic malignancies and selected solid tumors that will be conducted in 4 parts. In the dose escalation phase (Part 1), subjects with advanced lymphomas will be enrolled in sequential dose cohorts to receive TTI-621 once weekly to characterize safety, tolerability, PK, and the maximum-tolerated dose (MTD). In the expansion phase (Part 2), subjects with a variety of hematologic malignancies and selected solid tumors will be treated at the recommended dose of TTI-621 as determined in phase 1a (Part 1) to further define safety and to characterize efficacy. In the expansion phase (Part 3), based on preliminary observations of response, 2 cohorts of subjects (1 cohort with cutaneous T-cell lymphoma (CTCL) and 1 cohort with peripheral T-cell lymphoma (PTCL)), will be evaluated separately for the potential to be further studied using the Simon 2-stage design.

In the phase 1b dose optimization of the study (Part 4), further dose escalation of TTI-621 will be pursued in patients with relapsed and/or refractory CTCL following a 3+3 escalation design and using a revised DLT criteria. The major revision to the DLT criteria as used in phase 1a relates to Grade 4 thrombocytopenia. The safety data collected thus far from phase 1a and ongoing phase 1b expansion (by data cut-off of 01 October, 2018) showed that related ≥ Grade 3 thrombocytopenia and platelet count decreased occurred in 11% and 9% of patients respectively. Thrombocytopenia appeared to be transient and in general recovered within a week prior to the next dosing. Thrombocytopenia was not found to be associated with increased incidence of bleeding and had limited impact on the study drug delivery (See Section 1.8.4 for details). Based on the data, Grade 4 thrombocytopenia will be revised to qualify as a DLT only when the event lasts longer than 72 hours.

A Safety Review Committee (SRC) oversees the safety of all phases of the study. During the phase 1b dose optimization part (Part 4) of the study, the SRC convenes at appropriate intervals to review all available safety data in a cohort, cumulative information from all dosed subjects, and any new preclinical information as in phase 1a. The SRC renders decisions on dose escalation and other safety aspects of the study. All actions of the SRC are documented in written minutes. During phase 1b dose expansion phase (Part 2 and 3), any significant safety and tolerability issues observed based on medical monitoring and pharmacovigilance signal detection can be discussed at SRC for recommendation on any actions to be taken. The SRC can also convene to discuss any individual patient cases brought forth for advice by the treating investigators or the sponsor. The SRC will extend its responsibility under Amendment 9 to review both safety and efficacy data to recommend a decision as to whether or when to proceed the Part 3 CTCL and PTCL cohorts to next stage per the Simon's 2-stage design and in collaboration with the timing of the Part 4 dose optimization phase of the study. The membership of the SRC may vary between different phases of the study and will be documented in the Safety Committee Charter document.

Phase 1a Escalation (completed, as of amendment 9)

A minimum of 3 subjects will be treated in each cohort in a conventional 3 + 3 design, starting at Cohort 1. Given the potential risk for cytokine release syndrome, the first subject in each dosing cohort will be treated and observed for 72 hours before the next subject can receive their first infusion of TTI-621. (Cohort 0 represents a contingency de-escalation dose level in the event that tolerance issues are encountered in Cohort 1). Subjects will receive TTI-621 at the assigned dose once weekly for 3 weeks of treatment/observation for DLT assessment as defined in the protocol. If DLT is encountered in 1 of 3 subjects within a particular cohort, 3 additional subjects will be treated at that dose level. Otherwise,

enrollment will proceed sequentially through the predefined cohorts. Based on the incidence of DLT, the MTD will be determined.

Phase 1b Expansion (ongoing, as of amendment 9)

In the expansion phase of the study (Part 2), the safety and preliminary anti-tumor activity of TTI-621 monotherapy at the recommended dose of TTI-621 as identified in the escalation phase were explored in up to 40 subjects per cohort type, as outlined in the table below. These cohorts included: indolent B-cell lymphoma (IBCL), aggressive B-cell lymphoma (ABCL), T-cell lymphoma (TCL), Hodgkin lymphoma (HL), chronic lymphocytic leukemia (CLL), multiple myeloma (MM), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), and small cell lung cancer (SCLC). A cohort of subjects with CD20-positive malignancies were enrolled and treated with TTI-621 in combination with rituximab. In addition, a cohort of subjects with classic HL (cHL) were treated with TTI-621 in combination with nivolumab. Intrasubject dose-intensification after initial exposure to the recommended dose from phase 1a may be permitted at investigator discretion during the course of the study.

An overview of monotherapy and combination treatments administered in the expansion phase (Part 2 and 3) is provided in the table below. Starting doses of TTI-621 are shown; intrasubject dose-intensification may be permitted as outlined in Section 6.5.4.

As of Amendment 9:

Dose expansion:

Part 2

- The following monotherapy cohorts are closed to future enrollment: IBCL, ABCL, HL, CLL, MDS, MPN, SCLC, AML,MM, TCL and ALL
- The cohorts with TTI-621 in combination with rituximab or nivolumab for subjects with CD20+ malignancies, and cHL, respectively, will remain open for enrollment until the planned slots are filled

Part 3

- Two cohorts are ongoing : CTCL and PTCL (consisting of T- and NK-cell neoplasms per WHO definition (Swerdlow et al., 2016) with overall response in each of the 2 cohorts (CTCL and PTCL) evaluated separately using the Simon 2-stage design
- Dose intensification to a maximum of 0.5 mg/kg/week will be required for all newly enrolled subjects per Section 6.5.4. following a ramp-up schedule (2 weeks of study treatment at 0.2 mg/kg followed by dose intensification between week 3 and week 8 at increments of 0.1 mg/kg/week as tolerated up to maximum dose of 0.5 mg/kg/week)

In summary, as of Protocol Amendment 9, enrollment will be limited to the following disease types: CD20+ NHL (in combination with rituximab), cHL (in combination with nivolumab), CTCL and PTCL.

	Expansion Cohort (n)	**TTI-621 Starting Dose (mg/kg/wk)**	**Combination Partner Dose**	**Mandatory Dose Intensification** Starting at Week 3 increase by 0.1 mg/kg/wk increments up to a maximum of 0.5 mg/kg/wk
Monotherapy	IBCL (closed)	0.2	NA	closed
	ABCL (closed)	0.2	NA	closed
	HL (closed)	0.2	NA	closed
	TCL (closed)	0.2	NA	closed
	CTCL (up to 35)	0.2	NA	Yes
	PTCL (up to 35)	0.2	NA	Yes
	CLL (closed)	0.2	NA	closed
	ALL (closed)	0.2	NA	closed
	MM (closed)	0.2	NA	closed
	AML (closed)	0.2	NA	closed
	MDS (closed)	0.2	NA	closed
	MPN (closed)	0.2	NA	closed
	SCLC (closed)	0.2	NA	closed
Combination Therapy	Rituximab combination: CD20-positive malignancy (up to 40)	0.1	375 mg/m^2/wk for up to 8 cycles[a]	Yes
	Nivolumab combination: cHL (up to 15)	0.1	per FDA approved package insert for cHL[b]	Yes

Planned Dose Escalation Levels

		TTI-621 dose (mg/kg) DLT evaluation period		
Level	**N**	**Week 1 [b]**	**Week 2**	**Week 3**
0	3 (+ 3)	0.2	0.5	0.5
1[a]	3 (+ 3)	0.5	0.5	0.5
2	3 (+ 3)	0.7	0.7	0.7
3	3 (+ 3)	1.0	1.0	1.0
4	3 (+ 3)	1.4	1.4	1.4

[a] Level 1 = starting dose

[b] If de-escalation to Level 0 is required, all subsequent cohorts will start with a priming dose of 0.2 mg/kg at week 1 followed by the respective dose level escalation increments (to 0.7, 1.0, 1.4 mg/kg) at week 2 or subsequent weeks, as applicable, based on SRC decision.

The selection of the starting dose level and planned escalation cohorts will be guided by the dose intensification experience collected so far during the phase 1b expansion phase of this study. As of 26 November 2018, in Part 2, 12 T Cell Lymphoma patients were initially dosed at the recommended dose of 0.2 mg/kg and then dose intensified up to 0.5 mg/kg at the investigator discretion (ID). In Part 3 (A8), 14 T Cell Lymphoma patients have been treated per protocol-defined ramp-up schedule (2 weeks of study treatment at 0.2 mg/kg followed by dose intensification between week 3 and week 8 at increments of 0.1 mg/kg/week as tolerated up to maximum dose of 0.5 mg/kg/week). Among these patients who were exposed to 0.5 mg/kg of TTI-621, 22 patients (11 ID; 11 A8) had both pre and post-dose platelet assessments on W1D1 after receiving TTI-621 0.2 mg/kg. A total of 17/22 patients (11 ID; 6 A8) had both pre and post-dose platelet assessments at Weeks 5-30 after receiving 0.5mg/kg. Median pre- and post-dose platelet values following 0.2mg/kg and 0.5 mg/kg doses were 257/123, and 234/188, respectively. Grade 4 post-dose platelet levels occurred in 1 patient each following 0.2 mg/kg and 0.5 mg/kg TTI-621 doses; 5% (1/22) versus 6% (1/17), respectively (See Section 1.8.4). In addition, related adverse events (AEs) were generally comparable or less frequent following 0.5 vs. 0.2 mg/kg doses.

In the starting dose cohort (0.5 mg/kg), the first 3 patients will be treated sequentially to allow close monitoring of toxicity and timely dose adjustment if needed. The third patient will not start the study treatment until the first and second patient, respectively, have completed the initial two weeks of study treatment and had no observation of treatment-emergent adverse events (TEAE) meeting DLT criteria. If the first or second patient experiences a DLT event within the first two weeks of treatment, de-escalation to Level 0, a priming dosing regimen, will be considered per SRC discussion and decision. A priming regimen refers to a dosing regimen that involves a lower priming dose used during the initial week(s) of treatment followed by further dose escalation to a higher and stable dose for continued use throughout the course of the study. At Level 0, patients will be dosed at 0.2 mg/kg for the first week and then receive a stable dose of 0.5 mg/kg for the remainder of the study.

If Level 0 is determined to be tolerable per 3+3 schema, further escalation of doses beyond 0.5 mg/kg in Week 2 and beyond will be considered, as part of the priming dosing regimen. The same dose escalation increment (to 0.7, 1.0, and 1.4 mg/kg) may be followed after the initial week of exposure to 0.2 mg/kg.

A DLT is defined in phase 1b dose optimization (Part 4) as any of the following TEAEs that occur during the 3-week DLT period (including pre-dose tests on Day 22) and that are considered at least possibly related to study treatment by the investigator. Note that any AEs for which the relationship to study treatment cannot be ruled out should be considered possibly related:

- Grade 4 thrombocytopenia ($<25 \times 10^9$/L) lasting >72 hours or a platelet count $\leq 10 \times 10^9$/L at any time
- $\geq$ Grade 3 thrombocytopenia with bleeding (except epistaxis or gingival bleeding that is less than 24 hours in duration and does not require medical intervention, or normal menses) or requiring platelet transfusions

- Grade 4 anemia, unexplained by underlying disease
- Grade 4 neutropenia lasting >72 hours
- Grade 3 febrile neutropenia lasting >72 hours
- Grade 4 febrile neutropenia
- Grade 3 or higher non-hematologic toxicity with the following exceptions:
  - Grade 3 nausea and/or vomiting lasting <72 hours with standard supportive care
  - Transient Grade 3 fatigue lasting ≤72 hours
  - Transient asymptomatic Gra de 3 laboratory abnormalities considered not clinically significant following agreement between investigators and the sponsor's medical monitor and that last <72 hours with standard supportive care
- Other ≥ Grade 2 TTI-621-related non-hematologic toxicities that, in the opinion of the investigator, require a dose reduction or discontinuation of TTI-621

The major revision of the DLT criteria in comparison to those in phase 1a is that Grade 4 thrombocytopenia is no longer a DLT unless it lasts for more than 72 hours. This revision is based on a safety analysis of 179 patients by a data cut of 01 October, 2018. The majority of patients (143; 80%) had abnormal platelet counts reported at 1 or more timepoints post-dose, with 49 subjects (27%) experiencing Grade 4 decreases, including both TTI-621-induced events, and events resulting from the underlying hematologic malignancies. As shown in Figure 1-3 (See Section 1.8.4), reduced platelet counts that occurred on dosing days generally recovered within the week prior to the next dose. Overall, pre-infusion platelet counts remained stable over the course of the study. Due to the transient and reversible nature of the thrombocytopenia, no apparent increase in the incidence of bleeding has been observed on study (Table 1-1, Section 1.8.4). A total of 24/179 subjects (13%) experienced a treatment-emergent bleeding event in Study TTI-621-01 (see Table 1-1, Section 1.8.4). Overall, 20/179 subjects (11%) experienced Grade 1 or 2 events and 4 subjects (2%) had Grade 3 events. Grade 3 hemorrhage events were considered treatment-related for 3 subjects (2%). No Grade 4 hemorrhage events were reported. Therefore, relaxing the original DLT criteria is appropriate after the clinical significance of thrombocytopenia is better a ssessed with an expanded safety data set.

The MTD is defined as the dose level immediately below the lowest dose that at which 2 or more of either 3 or 6 patients experienced a DLT during the 3-week DLT period. At least 6 patients must be treated at the putative MTD, with no more than 1 incidence of DLT. AEs that occur after the 3-week DLT period or cumulative toxicities will be considered in the final designation of MTD.

If MTD is not reached after completion of all planned dose escalation levels, a decision will be made in consultation with the SRC, to either continue further escalation at a maximal 50% escalation increment, or dose escalation will be halted. A maximum assessed dose (MAD) could be used in lieu of the MTD. The SRC will review the totality of the safety, tolerability, PK, PD, and preliminary efficacy data (if available) before making this decision.

In addition to MTD/MAD determination, SRC will review the totality of cumulative toxicity and tolerability data in balance against the PK, PD and preliminary efficacy data. If a biologically active dose appears to be lower than MTD/MAD or if the MTD/MAD results in dose modification due to tolerability that limits continued dose exposure and in turn compromise the potential efficacy gain, a recommended phase 2 dose of TTI-621 lower than MTD/MAD can be determined for future single agent studies. Minimally 6 patients will need to be evaluated at the recommended phase 2 dose before formal designation.

After MTD/MAD or recommended phase 2 dose (if different from MTD/MAD) is determined, an additional 6 patients will be enrolled and treated at this dose level to form a safety expansion cohort of a total of 12 patients (including the 6 patients treated at the designated phase 2 dose before the dose selection). Preliminary efficacy will also evaluated in this cohort of patients.

The initiation of phase 1b dose optimization will occur after the closure of enrollment to Stage 1 of Part 3 CTCL cohort per Simon's 2-stage design. The proceeding of the Part 3 CTCL and PTCL cohort will follow the criteria as described per Simon's 2 stage design (Amendment 8). Other effica cy measures such as durability of response and disease control, safety signals in balance of clinical benefit, and evolving competitive landscape that impact the desirable efficacy assumption used in the Simon's 2 -stage design, may influence the decision by the sponsor whether to proceed these cohorts to Stage 2.

Additionally, in the context of Part 4 dose optimization introduced in Amendment 9, the following options will be considered and decisions regarding whether and/or when to proceed with the two Part 3 cohorts to

Stage 2 in relation to Part 4 dose optimization cohort will be made in a data-driven manner. Under this circumstance, SRC will review and discuss both safety and efficacy data and make recommendation to sponsor for final decision.

- Proceeding to Stage 2 may be halted until the completion of the phase 1b dose optimization (Part 4). At that time, the efficacy from Stage 1 in the Part 3 CTCL cohort will be assessed against that of the safety expansion cohort (when available) in CTCL patients in Part 4. The decision regarding which dose regimen to use for further clinical evaluation of single-agent TTI-621 in CTCL, PTCL, and/or other indications (the ramp-up schedule used in Part 3 vs selected dose regimen in Part 4) will depend on safety and the efficacy signal observed in association with these two dose regimens in CTCL. If the selected dose regimen in Part 4 is chosen, the sponsor may decide to stop the Simon's 2 stage study plan and choose another form of continued evaluation including but not limited to starting a new study.
- Proceeding to Stage 2 may occur in parallel to Part 4 dose optimization. This option may be considered when the efficacy signal from Stage 1 not only surpasses the minimal response criteria per the Simon's 2-stage design but presents higher probability of surpassing the target response rate of 30% overall response rate (ORR). This parallel option is particularly amenable to the scenario where the Stage 2 of Part 3 PTCL cohort is proceeding together with Part 4 dose optimization in Part 4 due to different target patient populations for the two parallel cohorts.

MAJOR ELIGIBILITY CRITERIA:

Phase 1a Escalation

Histologically documented, measurable, advanced lymphomas, transfusion -independence

Phase 1b Expansion (Part 2 and 3)

Advanced malignancy: IBCL, ABCL, cHL, AML, ALL, MDS, MPN, SCLC, PTCL and CTCL; measurable disease who have relapsed or are refractory following at least 2 prior systemic therapeutic attempts (1 prior systemic attempt for PTCL). For CTCL, extracorporal photochemotherapy (ECP) will be considered a systemic therapy. Local radiation and topical agents are not systemic therapies.

Note: the following monotherapy cohorts have been closed to future enrollment: IBCL, ABC L, HL, CLL, MDS, MPN, SCLC, AML, MM, T Cell and ALL.

Phase 1b dose optimization (Part 4)

Histologically confirmed diagnosis of CTCL (both Mycosis Fungoides and Sezary Syndrome):

- Failed at least 2 prior systemic therapies for CTCL (Systemic therapy does not include local radiation therapy or topical agents)
- Malignancy is measurable per global CTCL criteria (Olsen, 2011)
- History of histologically-documented diagnosis of CTCL stage IB to IVB (Olsen, 2011)

All subjects

- Previously progressed on, or currently progressing on standard anticancer therapy or for whom no other approved conventional therapy exists; male or female 18 years or older; Eastern Cooperative Oncology Group (ECOG) status of 0, 1, or 2; adequate hematologic, hepatic, renal, and coagulation function; fresh or archived tumor tissue available for immunohistochemistry; recovery from prior treatments and/or surgeries; no history of hemolytic anemia or bleeding diathesis.
- Subjects with AML M3 using the French American British (FAB) classification (i.e., acute promyelocytic leukemia [APL]) are excluded from this trial.

PLANNED SAMPLE SIZE:

Eighteen subject enrolled in phase 1a , and up to approximately 285 for the entire study including approximately 25 subjects in phase 1b dose optimization phase (Part 4).

TREATMENT PROCEDURES:

Subjects in the escalation phase will receive the assigned dose level of TTI-621 once weekly. TTI-621 will be infused in 250 mL of normal saline over 60 minutes. Vital signs will be measured and subjects will be monitored for possible infusion reactions. In the absence of disease progression, subsequent TTI-621 doses may be delivered if both clinical and laboratory AEs have resolved to Grade 1 or better (or to baseline grade if pre-existing) with the exceptions listed in Section 6.5.

Subjects in the expansion phase Part 2 will receive TTI-621 using the initial monotherapy MTD dose as identified in the escalation phase (0.2 mg/kg) as a starting dose. Subjects in the combination treatment cohorts will receive a starting dose of 0.1 mg/kg TTI-621 together with the combination partner agent. Subjects will receive the assigned dose level of TTI-621 once weekly. Subsequent TTI-621 doses will be delivered if both clinical and laboratory AEs have resolved per Section 6.5.3. Dose delays and/or reductions in individual subjects may be instituted as appropriate.

All newly enrolled subjects in the expansion phase Part 3 will undergo dose intensification weekly to a maximum dose of 0.5 mg/kg/week as tolerated in 0.1 mg/kg/week increments starting at Week 3. Dose modifications for TTI-621 should be instituted per Section 6.5.

Subjects in the phase 1b dose optimization phase (Part 4) will be enrolled in additional TTI-621 dose escalation cohorts, starting with level 1 (dose of 0.5 mg/kg) given once weekly. Following a 3+3 escalation design and using a revised DLT criteria, enrollment will continue through level 2 (starting dose of 0.7 mg/kg), level 3 (starting dose of 1.0 mg/kg) and level 4 (starting dose of 1.4 mg/kg) respectively. In the starting dose cohort (0.5 mg/kg), the first 3 patients will be treated sequentially to allow close monitoring of toxicity and timely dose adjustment if needed. The second and third patient will not start the study treatment until the first and second patient, respectively, have completed the initial 2 weeks of study treatment and had no observation of TEAEs meeting DLT criteria. If a DLT is noted in level 1, there may be de-escalation to level 0 (priming dose of 0.2 mg/kg at week 1 followed by 0.5 mg/kg at subsequent doses) with progression through Levels 2, 3 and 4 using the dose priming approach of 0.2 mg/kg at week 1 followed by the respective level dose regimens at subsequent weeks.

Treatment for all parts of the study (Part 1-4) may continue until disease progression, unacceptable toxicity, or other reason for treatment discontinuation. For phase 1b expansion Parts 2-4, for patients who have been given weekly infusion of TTI-621 for more than a year and are receiving clinical benefit (objective response or clinically meaningful long-term stable disease), investigators may exercise their discretion to reduce the dosing frequency from weekly to bi-weekly following the discussion and approval from the sponsor or designees.

STUDY TESTS AND OBSERVATIONS:

Standard safety measurements include physical exam and body weight, ECOG score, clinical AEs, laboratory variables (hematology, serum chemistries, urinalysis, and coagulation), electrocardiogram (ECG), and vital signs. Additional safety tests relevant to the biology of TTI-621 include evaluation of the incidence of antibodies to TTI-621. Quality of life (QOL) will be measured by the FACT-G questionnaire, (all tumor types), and using the SKINDEX29 questionnaire (subjects with CTCL).

Disease assessments will be performed as per Appendix D. Table 3. Blood will be taken serially for PK assessment. Additional blood samples will be taken for PD and biomarkers such as flow cytometric assessment of leukocyte subpopulations, receptor occupancy, and soluble cytokines/chemokines.

STUDY ENDPOINTS:

Phase 1a Escalation

- Primary: incidence and severity of AEs
- Secondary: PK profile, PD, ADA

Phase 1b Expansion (Part 2 and 3)

- Part 2 and 3 Primary: incidence and severity of AEs
- Part 2 and 3 Secondary: PK profile, PD, ADA, ORR, duration of response (DOR), and progression-free survival (PFS)
- Part 3 endpoints: CTCL and PTCL: organ system ORR - 2 analyses within each cohort

Phase 1b Expansion Dose Optimization (Part 4)

- Primary: incidence and severity of AEs
- Secondary: PK, PD, ADA, ORR, DOR, organ system overall response rate (Olsen, 2011)

STATISTICAL METHODS:

Safety Analyses

Safety analyses will be conducted using all dosed subjects. The results of the safety analyses will be presented by study phase. For the escalation phase, tabulations will be provided by dose cohort and overall. For the expansion phase, tabulations will be provided by disease cohort and overall. Some safety analyses may be performed based on all treated subjects combined.

TEAEs reported during the study will be tabulated and listed by MedDRA System Organ Class and preferred term. Tables will display number and percentage of subjects with the event for the following categories: all AEs, events considered related to study drug, events by severity, DLT, events occasioning treatment modification, and serious adverse events (SAEs). For the escalation phase, the observed DLT rate in each dose cohort will be calculated by the crude proportion of subjects who experienced DLT, accompanied with a 95% exact binomial CI.

Hematology and serum chemistries will be summarized using conventional summary statistics (mean, standard deviation, median, and range) for the following: baseline value, minimum and maximum post baseline values, average post baseline value, and last post baseline value. Standard shift tables will also be prepared presenting worst post baseline toxicity grade vs baseline. Incidence of subjects with ADA will be summarized descriptively. Laboratory values acquired during the immediate post-infusion period will be presented separately.

Vital signs and ECG results will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range by time point in the same manner described for laboratory va lues.

Pharmacokinetic Analyses

PK parameters of TTI-621 will be calculated from concentration-time data using noncompartmental analyses. Parameters may include, as appropriate, $AUC_{0-\tau}$, $AUC_{0-\infty}$, Cmax, Tmax, t1/2, clearance, and volume of distribution. Results will be reported using conventional summary statistics. The relationship between TTI-621 exposure and various safety indices will be assessed. All final PK analyses will be defined in the final PK analysis plan and/or final Statistical Analysis Plan (SAP) as appropriate.

Efficacy Analyses

Efficacy analyses will be conducted using the Full Analysis Set and, where appropriate, the Per-protocol Set; in addition, the ORR will also be presented for the Response-Evaluable Set and will be estimated for each cohort evaluated in the expansion phase using disease-specific response criteria. The DOR will be calculated for a subject who achieves response, and is defined as the number of weeks from the start date of the response (and subsequently confirmed) to the first date recurrent or progressive disease is documented; subjects who are ongoing at the time of the analysis will have the last study visit date included as a censored value for the Kaplan-Meier analysis. If a subject dies, irrespective of cause, without documentation of recurrent or progressive disease beforehand, then the date of death will be used to denote the response end date. PFS is defined as the number of weeks from the date of the first dose of study drug to the earliest of documented recurrent or progressive disease or death due to any cause without prior progression. DOR and PFS will be summarized descriptively using the Kaplan-Meier method with 95% CI calculated using Greenwood's formula. Median follow-up for each endpoint will be estimated according to the Kaplan-Meier estimate of potential follow-up. The PFS rate at selected landmarks (e.g., 6 months) and corresponding 95% CIs will be estimated using the Kaplan-Meier method. Greenwood's formula will be used to calculate the standard errors of the Kaplan-Meier estimate and upper and lower limits of the 95% CI.

Pharmacodynamic measurements and biomarkers will be summarized using summary statistics and may be displayed graphically as appropriate. Subgroup analyses, which will be pre-specified in the SAP, may be conducted in the expansion phase of the study to explore the relationship between measures of anti-tumor activity and selected baseline biomarkers.

Phase 1b Part 3-Specific Analyses

Each of the 2 additional cohorts (CTCL and PTCL) will be evaluated separately for the potential to be further studied using the Simon 2-stage design. For the first stage, a total of 18 response-evaluable subjects will be reviewed in each cohort; if 2 or fewer responders are observed, enrollment in the respective cohort will be terminated. Otherwise, enrollment will continue to the second stage and an additional 17 subjects will be enrolled for a total of 35 response-evaluable subjects per cohort. At the end of the second stage, if 6 or fewer responders per cohort are observed, the drug will be rejected for further testing in this indication. The safety and efficacy assessments outlined above will be summarized for each cohort separately. If more than the required number of response-evaluable patients are available (i.e., >18 or >35), the first 18 or 35, respectively, would be used.

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DEFINITIONS OF ABBREVIATIONS AND TERMS

Abbreviation or Term	Definition
ABCL	aggressive B-cell lymphoma
ADA	antidrug antibodies
ADaM	Analysis Dataset Model
AE	adverse event
ALCL	anaplastic large-cell lymphoma
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AP/BP	accelerated phase/blast phase
APL	acute promyelocytic leukemia
AST	aspartate aminotransferase
AUC	area under the curve
auto-SCT	autologous stem cell transplantation
BUN	blood urea nitrogen
BV	brentuximab vedotin
CD47	transmembrane protein and the target of TTI-621
CFR	Code of Federal Regulations
cHL	classic Hodgkin Lymphoma
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CMML	chronic myelomonocytic leukemia
CMR	complete metabolic response
CP	chronic phase
CR	complete response/remission
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	cutaneous T-cell lymphoma
DIPSS	Dynamic International Prognostic Scoring System
DLT	dose-limiting toxicity
DNMT1	DNA methyl transferase 1
DOR	duration of response
EC	Ethics Committee
EC_{50}	effective concentration at one-half of the maximal response is obtained
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECP	extracorporal photochemotherapy

Abbreviation or Term	Definition
EOI	end of infusion
EOT	end of treatment
ET	essential thrombocythemia
FAB	French American British
Fc	region of an immunoglobulin molecule
FDA	Food and Drug Administration
FLC	free light chains
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HL	Hodgkin lymphoma
HLA	human leukocyte antigen
HNSTD	highest non-severely toxic dose
HSCT	hematopoietic stem cell transplantation
IBCL	Indolent B-cell lymphoma
ICH	International Conference on Harmonisation
ID	investigator's discretion
IFN	interferon
IgG1	immunoglobulin G1
IMID	immunomodulatory drug
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous(ly)
LCL	lower confidence limit
LDH	lactate dehydrogenase
MABEL	minimal anticipated biological effect level
MAD	maximum assessed dose
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MF	Mycosis Fungoides
MM	multiple myeloma
MPN	myeloproliferative neoplasms
MPN-AP/BP	accelerated phase/blast phase myeloproliferative neoplasm
MPN/MDS	myeloproliferative/myelodysplastic overlap neoplasms
MRD	minimal residual disease
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NOS	not otherwise specified
ORR	objective/overall response rate

Abbreviation or Term	Definition
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamics
PD-1	programmed death-1
PD-L	programmed death ligand
PET	probability of early termination
PFS	progression-free survival
PK	pharmacokinetics
PMR	partial metabolic response
Post-ET	post-essential thrombocythemia
Post-PV	post-polycythemia vera
PR	partial response/partial remission
PTCL	peripheral T-cell lymphoma
PV	polycythemia vera
Q	every (e.g., Q2 weeks = once every 2 weeks)
QOL	quality of life
RAEB	refractory anemia with excess blasts
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SCLC	small cell lung cancer
SDTM	Study Data Tabulation Model
SFU	safety follow-up
SIRPα	signal regulatory protein alpha
SIRPα-IgG1 Fc	fusion protein consisting of the binding domain for CD47 (SIRPα) and a region of human IgG1 (Fc)
SRC	safety review committee
SS	Sézary syndrome
$t_{½}$	terminal half-life
TEAE	treatment-emergent adverse event
TCL	T-cell lymphoma
T_{max}	time of maximum concentration
TSH	thyroid-stimulating hormone
TTI-621	investigational product (SIRPα-IgG1 Fc)
ULN	upper limit of normal
WBC	white blood cell

1. INTRODUCTION

1.1 Hematologic Malignancies

Non-Hodgkin lymphoma (NHL), which together with Hodgkin lymphoma (HL) comprises the broad class of malignant lymphomas, is the most prevalent hematologic malignancy in the US, representing approximately 4% of all malignancies in both incidence and deaths per year (National Cancer Institute, 2015). Approximately 72,000 new cases of NHL will be diagnosed in 2015 and approximately 20,000 patients will die of their disease (Siegel et al., 2015).

NHL is further subdivided into two distinct prognostic groups: indolent and aggressive lymphomas. Indolent or low-grade subtypes have a relatively good prognosis with a median survival as long as 20 years; however, patients presenting with advanced disease are generally not curable with standard therapies. Patients with early-stage indolent NHL can often obtain disease control with radiation therapy alone, while patients with advanced disease often require systemic chemotherapy.

Aggressive or high-grade NHL often presents clinically in a more symptomatic manner than indolent lymphoma, but a considerable number of these patients can be cured using intensive combination chemotherapy regimens. The standard treatment for patients with aggressive lymphoma who do not obtain a complete response with frontline treatment — or for those who relapse — is intensive salvage chemotherapy followed by autologous stem cell transplantation (auto-SCT). Not all patients are suitable candidates for this aggressive treatment option. In addition, relapsed or progressive disease after auto-SCT occurs in more than 50% of patients with NHL (Philip et al., 1995); for these patients, prognosis is poor, with a median overall survival of 7 to 11 months (Paltiel et al., 2003). Currently there is no consensus treatment for patients who have relapsed or refractory disease after auto-SCT.

Across the disease spectrum, malignant lymphoma continues to represent an unmet medical need. Given the few treatment options available for patients with relapsed or refractory lymphoma, novel therapies providing clinical benefit are needed.

1.2 Cutaneous T-cell Lymphoma

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of extranodal lymphomas, which includes the 2 main subtypes, mycosis fungoides (MF) and Sézary syndrome (SS). Categorization of CTCL is based on the International Society for Cutaneous Lymphomas/European Organization for Research and Treatment of Cancer

(ISCL/EORTC) classification system (Olsen et al., 2011), which stratifies risk based on tumor, node, metastasis, and blood (TNMB) staging and provides prognostic information, with limited-stage disease conferring the longest median overall survival. Skin-directed therapies are preferred in the management of limited-stage disease, whereas advanced-stage disease requires systemic therapies. CTCL is characterized by variable CD30 over-expression; therefore, recently approved therapies include the CD30-directed antibody-drug conjugate brentuximab vedotin (BV). In an open-label, randomized phase 3 trial, BV was associated with an improved 4-month overall response rate (ORR) compared to physician's choice of therapy (4-month ORR of 56.3% versus 12.5%) (Prince et al., 2017). CTCL however, remained a resistant malignancy with a median PFS of 16.7 months in the BV arm, and 38/64 patients in the BV arm received subsequent anti-cancer therapy.

In a global, open-label, randomized trial in patients with previously treated CTCL, the anti-CCR4 antibody, mogamulizumab, demonstrated an improved ORR versus the histone deacetylase inhibitor, vorinostat (28% versus 4.8%, respectively), with the most pronounced improved ORR in patients with SS (37% [mogamulizumab] vs 2.3% [vorinostat]) (Kim et al., 2017). The median PFS was 7.7 months vs 3.1 months for mogamulizumab and vorinostat, respectively.

Other approved therapies for CTCL include bexarotene, vorinostat, romidepsin and pralatrexate with ORRs of approximately 20-30%. As demonstrated by the aforementioned clinical trials, novel therapeutic options are needed for patients whose CTCL recurs following approved therapies. Preliminary data with TTI-621 in both the intravenous and intratumoral studies suggests that CD47 blockade with an IgG1 Fc decoy agent may provide a therapeutic option for those with advanced and large-cell transformed disease, with several highly refractory patients experiencing objective responses in the phase 1b T-cell cohort.

1.3 Peripheral T-cell Lymphoma

Aggressive peripheral T-cell lymphomas (PTCLs) per WHO 2016 classification, can be subdivided into those of primarily nodal origin and those that typically present in specific extranodal sites and are often associated with characteristic clinical syndromes (Swerdlow et al., 2016). Anaplastic large-cell lymphoma (ALCL) is the one of the more common types of aggressive PTCL. In 65% of cases, ALCL is characterized by the ALK mutation which impacts survival. In the 1314 patient experience of The International Peripheral T-Cell Lymphoma Project, Savage and colleagues reported that the 5-year OS (70% vs. 49%) and 5-year failure-free survival (60% vs. 36%) both favored patients with ALK-positive ALCL (Savage et al., 2008). Additionally, they found that the 5-year failure-free survival rate for ALK-negative ALCL was superior when compared with PTCL not otherwise specified

(NOS): 36% vs 20%; p=0.012, with an OS of 49% vs 32%; p=0.032. PTCL-NOS is characterized by aggressive disease, short duration of response, and poor overall survival. A recent review concluded that PTCL patients with recurrent disease display a "dismal prognosis with their therapy representing an unmet medical need as best treatment strategy is yet to be determined" (Broccoli and Zinzani, 2017). Preliminary results with TTI-621 have demonstrated anti-tumor activity in several patients with a variety of subtypes of relapsed or refractory PTCL.

1.4 CD47 and SIRPα

CD47 is a cell-surface protein expressed on multiple normal cell types and often at high levels on many malignant tumor cells. CD47 interacts with several different proteins and is involved in a wide variety of physiologic processes including platelet and neutrophil activation, T-cell function, regulation of vascular signaling by nitric oxide, inhibition of dendritic cell activity, and inhibition of monocyte activation. CD47 binds to signal regulatory protein alpha (SIRPα) on the surface of macrophages thereby transmitting a signal that inhibits the ability of macrophages to phagocytose the cell (Weiskopf and Weissman, 2015).

SIRPα is a transmembrane glycoprotein receptor consisting of 3 extracellular immunoglobulin-like domains and a cytoplasmic tail that triggers phosphatase-mediated signaling. SIRPα is found on macrophages, monocytes, granulocytes, dendritic cells, and neurons (Adams et al., 1998).

1.5 Regulation of Phagocytic Activity

Macrophage-mediated phagocytosis is regulated by both positive and negative signals. Normally, macrophages recognize pro-phagocytic signals that are present on tumor cells and absent on normal cells that trigger engulfment and destruction. CD47, which transmits an anti-phagocytic signal through SIRPα, is an important mechanism by which malignant cells escape immune-mediated clearance. Although the precise mechanism by which the CD47-SIRPα axis inhibits phagocytosis is not fully understood, it is thought to involve deactivation of the contractile cytoskeletal activity involved in pulling the target cell into a macrophage for ingestion (Tsai and Discher, 2008).

High levels of CD47 have been found to correlate with poor clinical prognosis in patients with a number of cancer types, including most hematologic malignancies (Chao et al., 2011; Chao et al., 2010; Jaiswal et al., 2009; Majeti et al., 2009). For example, OS was significantly lower for patients with diffuse large B-cell lymphoma and mantle cell lymphoma who had elevated CD47 expression. Similarly, patients with chronic

lymphocytic leukemia (CLL) that expressed high levels of CD47 experienced a significantly worse event-free survival compared with those whose tumor expressed lower expression levels (Chao et al., 2010).

Phagocytosis of tumor cells, including small cell lung cancer (SCLC) cells, may be experimentally increased by disrupting the CD47-SIRPα interaction by means of anti-CD47 antibodies. Several developmental programs are underway to explore this possible therapeutic approach. In addition, CD47 blockade has been shown to augment rituximab potency in preclinical models (Chao et al., 2010). Preclinical studies have also demonstrated that the combination of a CD47 antagonist with programmed death-ligand (PD-L)-1 blockade resulted in tumor control and increased survival compared with either agent alone (Sockolosky et al., 2016).

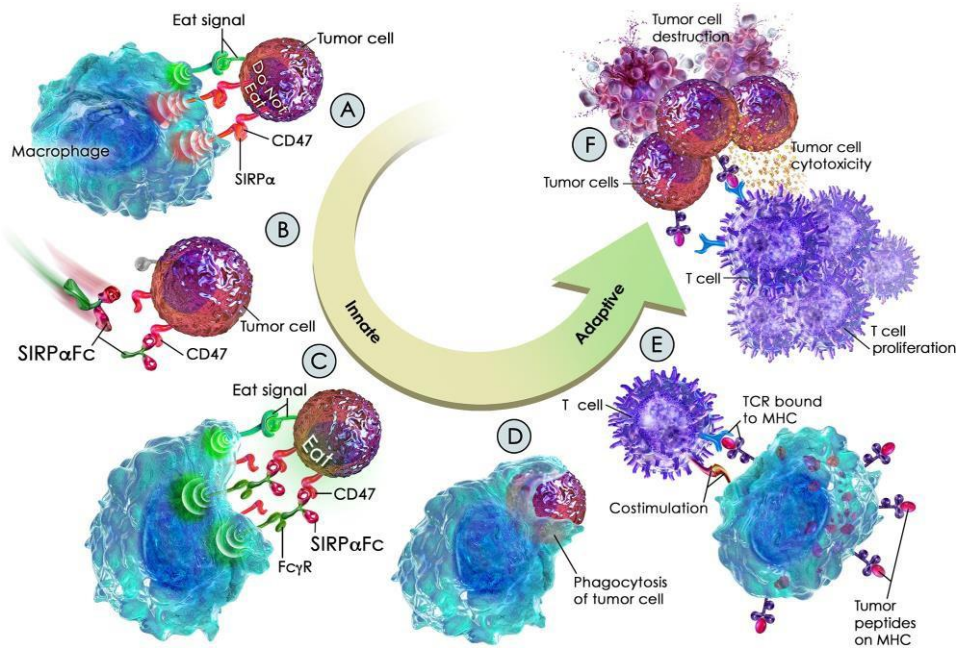
1.6 TTI-621

Trillium Therapeutics Inc. (Trillium) is developing TTI-621 (SIRPα-IgG1 Fc), a soluble recombinant fusion protein created by combining the sequences encoding the N-terminal portion of human SIRPα with the Fc region of human IgG1. The SIRPα region interacts with its ligand CD47, while the Fc region binds to macrophage Fcγ receptors. TTI-621 functions as a decoy receptor, binding CD47 on the surface of the tumor cells and blocking its anti-phagocytic signal, allowing the macrophage to ingest the malignant cell. The Fc region of TTI-621 may also assist in the activation of macrophages through engagement of Fcγ receptors.

1.6.1 Mechanism of Action

The proposed mechanism of action for TTI-621 is illustrated in Figure 1-1. Tumor cells express high levels of the CD47 “do not eat” signal, which suppresses phagocytosis by engaging SIRPα on the surface of macrophages, overriding any pro-phagocytic (“eat”) signals (Step A). The decoy receptor TTI-621 binds to CD47 on the surface of tumor cells (Step B) and engages activating Fc-gamma receptors on macrophages (Step C). The combination of CD47 blockade and activating signals triggers macrophage phagocytosis of tumor cells (Step D). Macrophages then process the internalized tumor cells, resulting in the presentation of tumor antigen peptide-MHC complexes at the cell surface (Step E), triggering T cell activation and tumor cell destruction (Step F). Thus, blockade of CD47 by TTI-621 is proposed to activate both the innate and adaptive immune systems.

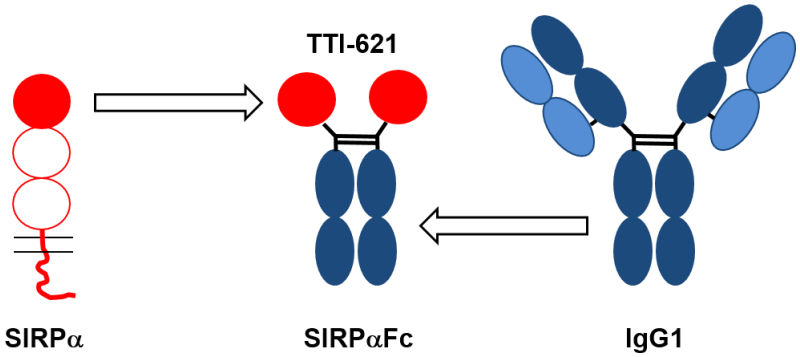
Figure 1-1: Proposed TTI-621 Mechanism of Action



1.6.2 Chemistry and Description

TTI-621, which has a molecular weight of 76,677 daltons, is a homodimer consisting of identical polypeptides each containing 345 amino acids and linked by a disulfide bond (Figure 1-2). The protein is glycosylated through N-linkage. TTI-621 is expressed and secreted by a genetically engineered Chinese Hamster Ovary cell line.

Figure 1-2: Schematic of TTI-621



TTI-621 consists of the N-terminal domain of human SIRPα (red) linked to a human IgG1 Fc region (blue). The hinge and inter-chain disulfide bonds are represented in black.

TTI-621 as formulated for clinical trial use is described in Section 6.1. Additional information is found in the Investigator's Brochure.

1.6.3 Nonclinical Pharmacodynamics

TTI-621 bound to human hematopoietic tumor cell lines and primary tumor samples with an effective half-maximal concentration (EC_{50}) of 14–807 nM (1–62 µg/mL). Comparable binding was also observed on normal human white blood cells and platelets, although there was extremely low binding to human red blood cells (RBCs) despite their abundant expression of CD47. This unusually low level of binding may be a consequence of CD47 association with the RBC cytoskeleton and resulting lack of membrane mobility, which may preclude the formation of high-affinity TTI-621:CD47 clusters on the RBC surface.

TTI-621 cross-reacts with CD47 from cynomolgus macaques (97.6% amino acid sequence homology to humans) and binds strongly to monkey RBCs. This makes the cynomolgus monkey a suitable model for studying the pharmacology and toxicology of TTI-621. TTI-621 did not bind rat or mouse cells, which is consistent with the known species selectivity of human SIRPα.

The ability of TTI-621 to promote macrophage-mediated destruction of human tumor cells was assessed in vitro. TTI-621 was shown to potently trigger the phagocytosis of a variety of hematopoietic tumor cell lines and primary patient samples. The biological activity of TTI-621 in this system occurred at an average concentration of 11 nM (0.84 µg/mL), representing the anticipated active dose of TTI-621. TTI-621 did not provoke the phagocytosis of normal blood-derived monocytes. This specificity for cancer cells likely results from the expression of requisite pro-phagocytic signals on malignant cells that are absent on normal cells.

TTI-621 was evaluated in an in vivo acute myeloid leukemia (AML) xenograft model in which patient-derived tumor cells were injected directly into the femur of preconditioned NOD.SCID mice. Antileukemic activity was observed in 4 of 5 AML samples tested. Profound reductions in tumor burden were observed in animals receiving 5 mg/kg TTI-621, with partial anti-tumor activity at 0.2 and 1 mg/kg doses.

The presence of CD47 on non-tumor tissue has the potential to bind SIRPα-IgG1 Fc and remove it from circulation (an antigen sink effect). Since TTI-621 does not cross-react with mouse CD47, it would not model the antigen sink effect that might ordinarily occur. Hence, a mouse surrogate fusion protein (TTI-508) was generated using the SIRPα sequence from NOD mice. This surrogate binds both mouse and

human CD47 and contains a mouse IgG2aFc region that allows for homologous Fc-Fcγ receptor interactions in mice. TTI-508 induced macrophage phagocytosis of a human tumor cell line in vitro with similar potency to TTI-621. In vivo, TTI-508 was highly active in the AML xenograft model, dramatically reducing tumor burden at a 1 mg/kg dose and exerting a partial effect at 0.2 mg/kg. TTI-508 was also highly efficacious in human B-cell lymphoma xenograft models when dosed at 10 mg/kg.

Collectively, the primary pharmacology studies demonstrated the following:

- TTI-621 bound to human $CD47^+$ tumor cells with EC_{50} values ranging from 14–807 nM (1–62 μg/mL) with nanomolar affinity.
- TTI-621 induced macrophage-mediated phagocytosis of a range of hematologic tumor cells but not of normal cells.
- TTI-621 bound strongly to cynomolgus monkey RBCs despite an inherently weaker binding affinity to monkey CD47.
- TTI-621 bound weakly to human RBCs but did not induce hemolysis or agglutination of human RBCs in vitro.

Secondary pharmacology studies of TTI-621 demonstrated the following:

- TTI-621 induced antibody-dependent cellular cytotoxicity (ADCC) of human tumor target cell lines but did not mediate complement-dependent lysis.
- TTI-621 was not directly cytotoxic to human tumor cell lines at concentrations up to 10 μM (767 μg/mL) and did not induce direct hemolysis of monkey or human RBC.
- TTI-621 did not provoke significant in vitro release of IL-2, IL-4, IL-10, IFN-γ or TNF-α, but did induce IL-6 and IL-8 release at levels above background in a minority of donor blood samples.
- TTI-621 bound strongly to human platelets but had no effect on platelet aggregation. Additionally, TTI-621 on its own did not affect the activation of human or monkey platelets. No inhibitory effect on agonist-induced platelet activation was observed for either species.

Additional information is found in the Investigator's Brochure.

1.6.4 Nonclinical Pharmacokinetics

Pharmacokinetic (PK) investigations were conducted in conjunction with both the Good Laboratory Practice (GLP) and non-GLP primate toxicology studies. Across all studies, TTI-621 doses ranged from 0.5 to 12.5 mg/kg. Dosing was intravenous (IV) with the exception of 1 cohort of male monkeys given TTI-621 subcutaneously (SC) in Study 5001009. In general, both maximum blood concentration (C_{max}) and area

under the curve $(AUC)_{0-\infty}$ increased in a more-than-dose-proportional manner. Mean terminal half-life ($t_{1/2}$) values between all cohorts after the Day 1 dose were extremely variable, ranged from 35.2 to 156 hours, or approximately 1.5 to 6.5 days. The variation in $t_{1/2}$ between cohorts did not appear to be a function of dose. SC dosing led to lower C_{max} and $AUC_{0-\infty}$ and longer time to C_{max} (T_{max}) values compared with IV dosing; however, $t_{1/2}$ and other parameters were similar between SC and IV administration.

Trends in the PK parameters of later time points were inconsistent and variable relative to Day 1, which was likely a consequence of the development of antidrug antibodies (ADA) in the majority of animals.

Additional information may be found in the Investigator's Brochure.

1.6.5 Toxicology

The toxicology program consisted of 5 studies: 3 non-GLP pilot dose-finding studies and 2 GLP IND-enabling studies, all conducted in cynomolgus monkeys.

A total of 86 monkeys were dosed with TTI-621 in these toxicology studies. TTI-621 was administered either via a 1-hour IV infusion or a SC injection over a range of concentrations between 0.5 mg/kg and 12.5 mg/kg. The IV dosing regimens tested across studies ranged from twice weekly to once every 2 weeks, while the SC dosing regimens ranged from 3 times weekly to once every 2 weeks. The majority of animals at the lower doses (0.5, 1, 1.25, 1.5 and 3 mg/kg) tolerated treatment well. There were no test article effects at the injection/infusion site and no measurable effects on the cardiovascular, respiratory, ophthalmologic, or nervous systems. Isolated animals at higher doses displayed clinical symptoms including hypo-activity, pallor, anorexia with or without weight decrease, general debility, and hypothermia.

Treatment-emergent and dose-related anemia — sometimes profound but reversible — was a consistent laboratory finding and many of the above clinical symptoms were attributed to effects of TTI-621 on the RBC compartment. These effects on clinical pathology demonstrated reversibility during the recovery phase. Six of the 86 animals receiving TTI-621 at doses ≥3mg/kg were pre-terminally sacrificed due to severe anemia (N=4) or hemorrhage (N=2). Anemia was not unexpected, as TTI-621 binds strongly to cynomolgus RBCs and CD47 is speculated to regulate the normal homeostatic clearance of RBCs by macrophages. Blockade of CD47 may therefore accelerate this clearance, as observed with CD47-blocking antibodies in non-human

primates. TTI-621 shows only minimal binding to human RBCs, and therefore the anemia observed in monkeys is thought to be less likely to occur in human subjects.

The highest non-severely toxic dose (HNSTD) for once-weekly IV dosing was determined to be 1 mg/kg, with anemia as the most consistent treatment-related effect. TTI-621 exhibits minimal binding to human RBCs in vitro; hence, significant anemia is not expected. However, the risk of treatment-emergent anemia in the clinical studies cannot be ruled out.

Additional information with descriptions of each study is found in the Investigator's Brochure.

1.7 Anticipated or Possible Risks in Human Subjects

Summary of Dose-Escalation Safety Data

Data from the first 18 subjects enrolled in the dose-escalation phase of the study show that TTI-621 has been reasonably well tolerated. Transient, dose-dependent decreases in platelets without clinical sequelae occurred in the hours following infusion in the majority of subjects exposed to TTI-621. Thrombocytopenia was relatively brief with recovery to baseline platelet counts by the next weekly dose and appeared attenuated with weekly TTI-621 exposure. Other Grade 3/4 cytopenias (monocytes, neutrophils, and lymphocytes) were also frequently observed; all were transient and resolved without sequelae.

The majority of subjects experienced mild to moderate infusion-related reactions (IRRs) that typically occurred after the first TTI-621 infusion only. IRRs were reported across all dose cohorts with no obvious dose relationship and occurred despite premedication with an antihistamine and acetaminophen.

Three subjects experienced reversible Grade 3 hypophosphatemia in the days following their first infusion of TTI-621. Hypophosphatemia in 1 of the 3 subjects was considered related to TTI-621 and was therefore reported as a DLT. The event rapidly resolved without intervention. Hypophosphatemia was considered unrelated to TTI-621 in the other 2 subjects and their phosphate levels were corrected by oral phosphate.

No subjects in either the 0.05 mg/kg/week or 0.1 mg/kg/week dose groups experienced dose-limiting toxicity (DLT). However DLTs were reported for 2 of 5 subjects treated at the 0.3 mg/kg/week dose: 1 subject with Grade 4 thrombocytopenia and 1 subject with Grade 4 thrombocytopenia and Grade 3 elevated alanine aminotransferase/aspartate aminotransferase (ALT/AST). Upon review of cumulative adverse events (AEs) and laboratory values, the Safety Review Committee (SRC) recommended proceeding with

enrollment at an intermediate dose level of 0.2 mg/kg TTI-621 (Cohort 2a), and to dose reduce all subjects participating in the 0.3 mg/kg cohort to the 0.2 mg/kg dose level (one subject was dose reduced to the 0.1 mg/kg dose level).

Seven subjects were subsequently enrolled in Cohort 2a, 6 of whom were DLT evaluable. One of the 6 DLT-evaluable subjects experienced a DLT of Grade 3 hypophosphatemia; therefore, the SRC declared 0.2 mg/kg as the MTD and enrollment to the expansion phase is currently underway. Similarly, a dose of 0.2 mg/kg/week in combination with rituximab was initially recommended for subjects enrolled in the combination treatment arm; however 1 subject treated with TTI-621 experienced an SAE of Grade 3 gastrointestinal bleed; therefore, current subjects receive an initial dose of 0.1 mg/kg TTI-621 administered together with the combination partner agent.

Safety Update

As of a data cutoff date of 01 October, 2018, a total of 179 subjects (177 unique individuals) had been enrolled in Study TTI-621-01: 18 subjects were enrolled in the dose-escalation phase and 161 subjects had been enrolled in the expansion phase. Two subjects were re-enrolled on Study TTI-621-01; these subjects were originally enrolled and treated in the dose-escalation phase of the study and were subsequently enrolled and treated in the expansion phase. Two additional subjects with CTCL who participated in Study TTI-621-02 and received local intratumoral treatment with TTI-621 in cutaneous lesions, enrolled on Study TTI-621-01 to receive systemic TTI-621 after completing treatment on Study TTI-621-02.

Overall, 166/179 subjects (93%) enrolled in Study TTI-621-01 experienced at least 1 treatment emergent adverse event (TEAE). TEAEs in 134/179 subjects (75%) were considered related to TTI-621 treatment by Investigators. The most frequently reported TEAEs were infusion-related reactions in 72 subjects (40%), chills in 33 subjects (18%), fatigue in 26 subjects (15%), thrombocytopenia in 26 subjects (15%), nausea in 21 subjects (12%), platelet count decreased in 20 subjects (11%), anemia in 18 subjects (10%), and pyrexia in 18 subjects (10%). A total of 59 subjects (33%) experienced a ≥ Grade 3 TEAE that was considered related to TTI-621. The most frequently reported treatment-related ≥ Grade 3 TEAEs were thrombocytopenia in 19 subjects (11%), platelet count decreased in 16 subjects (9%), anemia in 11 subjects (6%), neutropenia in 7 subjects (4%), neutrophil count decreased in 6 subjects (3%), white blood cell count decreased in 4 subjects (2%), and infusion-related reaction in 3 subjects (2%). All other treatment-related ≥ Grade 3 TEAEs were reported for ≤2 subjects.

Infusion-related reactions have been frequently reported in this study. The majority of reactions were Grade 1 or 2 and were reported across all dose cohorts with no obvious dose relationship and occurred despite premedication with an antihistamine and acetaminophen. Three subjects in the expansion cohorts of this study experienced ≥ Grade 3 infusion-related reactions; 2 of these events were reported as SAEs and resulted in TTI-621 discontinuation for 1 subject.

Thrombocytopenia/platelet count decreased were the most frequently reported ≥Grade 3 related TEAEs, occurring in 19/179 (11%) and 16/179 (9%) of subjects respectively. Thrombocytopenia/platelet count decreased occurred within 24 hours following infusion in majority of patients exposed to IV administration of TTI-621. Reduced platelet counts appeared transient and generally recovered within a week prior to the next dosing. Overall, pre-infusion platelet counts remained stable over the course of the study and no clinical sequela was observed (See Section 1.8.4).

Grade 3/4 cytopenias, including decreased monocytes, neutrophils, and lymphocytes, were observed and reported as laboratory abnormalities as well as TEAEs.

Treatment-related, Grade 3 or higher anemia was reported in 11 subjects receiving IV TTI-621. All events occurred in subjects with primary hematologic malignancies in which anemia is frequently caused by the malignancy itself (AML/MDS/MPN). No serious events of anemia were reported and anemia did not appear to be associated with increased destruction of erythrocytes.

See Section 9.5 for further details of anticipated risks and AEs of special interest.

1.8 Rationale for Selection of Doses

1.8.1 TTI-621 Monotherapy

The selection of the TTI-621 starting dose in human subjects was determined using a conventional HNSTD approach. The HNSTD for once-weekly administration of TTI-621 in the GLP toxicology study was 1 mg/kg. Using the standard 1/6 safety factor and applying a 0.32 multiple to convert the cynomolgus monkey mg/kg into a human equivalent dose resulted in a starting dose of 0.053 mg/kg. Thus, a starting dose of 0.05 mg/kg was proposed for this study. A similar starting dose was determined using a conservative minimum anticipated biological effect level (MABEL) calculation based on 10% receptor occupancy of human platelets (see Investigator Brochure).

1.8.2 Combination Therapy Cohorts

As outlined in Section 1.7, the starting dose for subjects in the TTI-621 plus rituximab expansion cohort is 0.1 mg/kg TTI-621 given weekly in combination with 375 mg/m2 rituximab. This dose of rituximab is the standard approved dose for patients with previously untreated NHL when given in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or other anthracycline-based regimens (Rituxan® [rituximab] package insert. San Francisco, CA: Genentech; and Rituxan® [rituximab] product monograph. Mississauga, Ontario: Hoffmann-La Roche Ltd.). There is no standard dose or schedule of rituximab in the relapsed/refractory setting; however, the selected dose and schedule has been safely and effectively employed in combination with various single- and multi-agent chemotherapy regimens for this patient population.

The starting dose for subjects in the combination TTI-621 plus nivolumab expansion cohort is 0.1 mg/kg TTI-621 given weekly in combination with 3 mg/kg nivolumab given every 2 weeks or at a fixed dose as per the approved package insert for patients with HL (OPDIVO® [nivolumab]. Princeton, NJ: Bristol-Myers Squibb Company and OPDIVO® [nivolumab] product monograph. Montreal, Canada: Bristol-Myers Squibb Canada).

1.8.3 Rationale for Intrasubject Dose-Intensification

In vitro studies suggest that increased CD47 receptor occupancy by TTI-621 is associated with increased macrophage-mediated phagocytosis of tumor cells—providing rationale for further dose intensification of TTI-621, as tolerated. Clinically, reversible thrombocytopenia has reliably and rapidly occurred after TTI-621 infusions. However, thrombocytopenia recovered without active management within a week and was asymptomatic (See Section 1.8.4). In Part 2, as of Amendment 6, intra-subject dose intensification was made permissible at investigator's discretion after initial treatment at the recommended dose of 0.2 mg/kg determined during phase 1a dose escalation.

As of 01 October 2018, TTI-621 dose intensification per Investigator discretion has been employed for 46 subjects enrolled on Study TTI-621-01. The most common treatment-related ≥ Grade 3 events, occurring in ≥ 2 patients experienced by these subjects following dose intensification were limited to Grade 3 or higher platelet count decreased (17.4%), anemia (8.7%), thrombocytopenia (4.3%), neutropenia (4.3%), neutrophil count decreased (4.3%) and white blood cell count decreased (4.3%).

Platelet decrease did not appear worse after dose intensification up to 0.5 mg/kg (Section 1.8.4). For these reasons, in Part 3, all patients in CTCL and PTCL cohorts will receive a standardized dose ramp-up regimen which includes initial two-weeks of 0.2 mg/kg treatment followed by cautious intrasubject dose intensification at an increment of 0.1 mg/kg per week up to 0.5 mg/kg within 5-8 weeks. Details regarding when dose intensification should be delayed or stopped due to AEs are is provided in Section 6.5.4.

1.8.4 Rationale for Phase 1b Dose Optimization (Part 4)

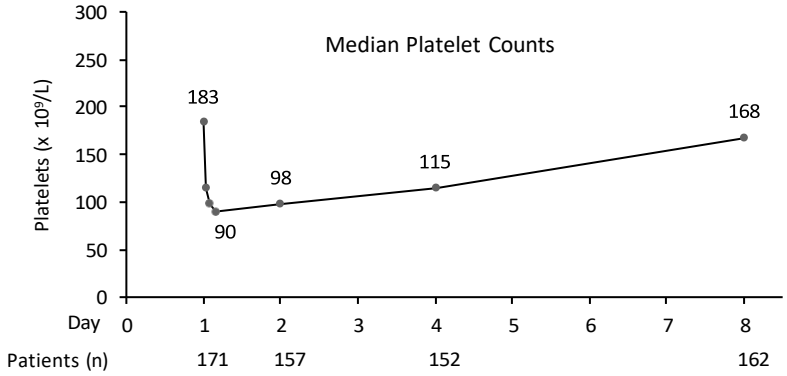
During phase 1a dose escalation (Part 1), weekly infusion of TTI-621 at 0.2 mg/kg was determined to be the MTD per 3+3 dose escalation as planned. Two Grade 4 events of asymptomatic thrombocytopenia were observed in 2/3 patients dosed at 0.3 mg/kg. Per the DLT criteria in phase 1a, these two events were determined to be a DLT which led to the conclusion that 0.3 mg/kg exceeded MTD. The majority of the patients treated during Phase 1b dose expansion Part 2 received weekly infusions of 0.2 mg/kg TTI-621. Based on a safety analysis of 179 patients by a data cut of 01 October, 2018, the majority of patients (143; 80%) had abnormal platelet counts reported at 1 or more timepoints post dose, with 49 subjects (27%) experiencing Grade 4 decreases, including both TTI-621-induced events, and events resulting from the underlying hematologic malignancies. As shown in Figure 1-3, platelet counts decreased acutely on dosing days but generally recovered within the week prior to the next dose. Overall, pre-infusion platelet counts remained stable over the course of the study. Additionally, due to the transient and reversible nature of the thrombocytopenia, no apparent increase in the incidence of bleeding has been observed on study. A total of 24/179 subjects (13%) experienced a treatment-emergent bleeding event (see Table 1-1).

Overall, 20/179 subjects (11%) experienced Grade 1 or 2 events and 4 subjects (2%) had Grade 3 bleeding events. Grade 3 hemorrhage events were considered treatment-related for 3 subjects (2%). No Grade 4 hemorrhage events were reported. Therefore, based on the expanded safety data in which the clinical significance of thrombocytopenia is now better understood, the original DLT criteria have been reassessed and revised. The major revision of the DLT criteria in comparison to those in Phase 1a is that Grade 4 thrombocytopenia is no longer a DLT unless it lasts for more than 72 hours. With this revision, the two original DLT events of Grade 4 thrombocytopenia would no longer be qualified as DLTs, so 0.3 mg/kg should not have exceeded MTD. Therefore, further dose escalation per revised DLT criteria to re-define MTD or recommended Phase 2 dose is warranted. This effort is further justified by the safety data collected thus far from selected patients who dose intensified on

study to doses higher than 0.2 mg/kg during phase 1b expansion. Exposure to higher doses up to 0.5 mg/kg appeared to be tolerable.

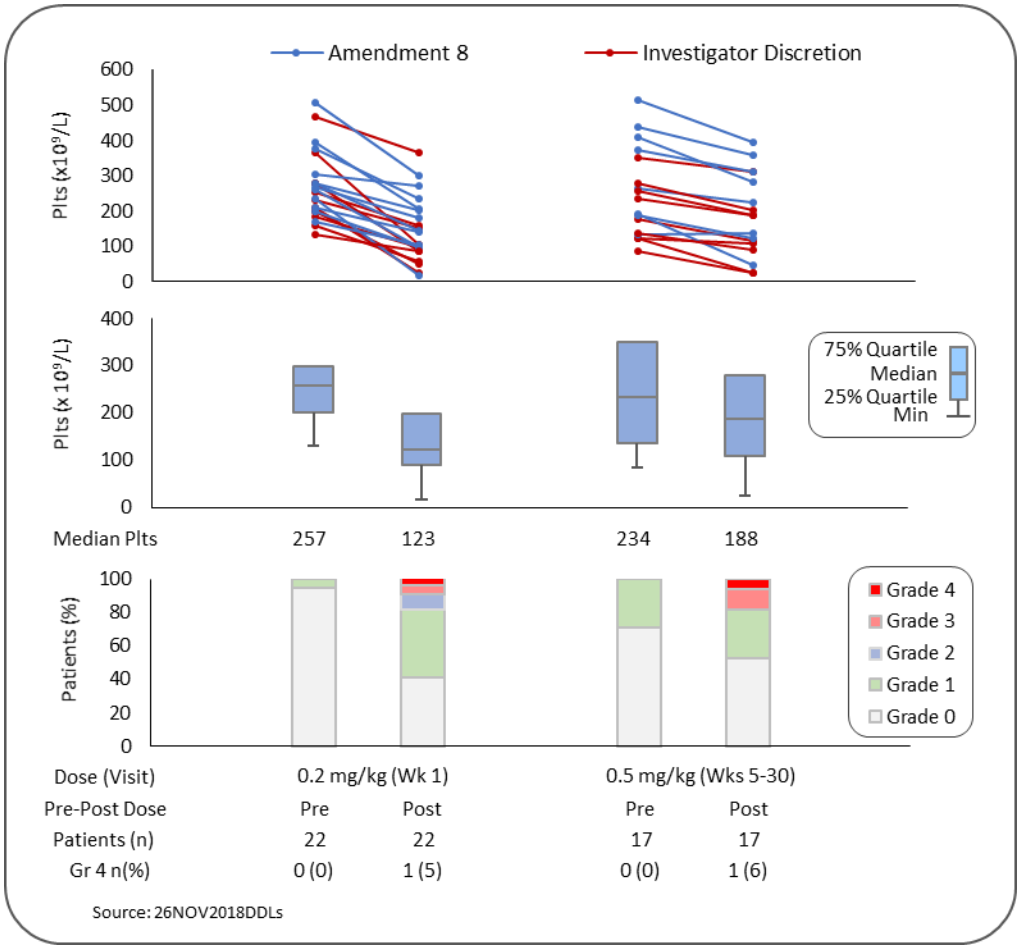
The selection of the starting dose level and planned escalation cohorts are guided by the dose intensification experience collected so far during the phase 1b expansion phase of this study. As of 26 November 2018, in Part 2, 12 T Cell Lymphoma patients were initially dosed at the recommended dose of 0.2 mg/kg and then dose intensified up to 0.5 mg/kg at the investigator discretion (ID). In Part 3 (A8), 14 T Cell Lymphoma patients have been treated per protocol-defined ramp-up schedule (2 weeks of study treatment at 0.2 mg/kg followed by dose intensification between week 3 and week 8 at increments of 0.1 mg/kg/week as tolerated up to maximum dose of 0.5 mg/kg/week). Among these patients who were exposed to 0.5 mg/kg of TTI-621, 22 patients (11 ID; 11 A8) had both pre and post-dose platelet assessments on W1D1 after receiving TTI-621 0.2 mg/kg. A total of 17/22 patients (11 ID; 6 A8) had both pre and post -dose platelet assessments at Weeks 5-30 after receiving 0.5mg/kg. Median pre- and post-dose platelet values following 0.2mg/kg and 0.5 mg/kg doses were 257/123, and 234/188, respectively. Grade 4 post-dose platelet levels occurred in 1 patient each following 0.2 mg/kg and 0.5 mg/kg TTI-621 doses; 5% (1/22) versus 6% (1/17), respectively. In addition, related AEs were generally comparable or less frequent following 0.5 vs. 0.2 mg/kg doses.

Figure 1-3: Pre-dose Platelet Counts During Week 1



Graph shows that the 0.2 mg/kg dose level, platelet counts decreased acutely on week 1 dosing days but generally recovered within the week prior to the next dose.

Figure 1-4: Pre and Post-Dose Platelet Levels following 0.2 and 0.5 mg/kg TTI-621



Patients with pre and post-dose platelet levels following administration of TTI-621 at 0.5 mg/kg had previously been treated at 0.2 mg/kg. Platelet values on the left side of the figure are from patients dosed at 0.2 mg/kg. Platelet values on the right side of the figure are from those patients that had their dose incrementally increased up to 0.5 mg.kg

Table 1-1: Treatment-Emergent Bleeding AEs (Safety Analysis Set)

Bleeding Adverse Event n (%)	Adverse Event Severity						Total n=179
	Grade 1		Grade 2		Grade 3		
	NR	R	NR	R	NR	R	
Subjects with any bleeding TEAE	11 (6)	9 (5)	3 (2)	0	2 (1)	3 (2)	24 (13)
Epistaxis	4 (2)	5 (3)	0	0	0	2 (1)	11 (6)
Gastrointestinal haemorrhage	0	0	0	0	2 (1)	1 (1)	2 (1)
Petechiae	2 (1)	0	0	0	0	0	2 (1)
Anal haemorrhage	1 (1)	0	0	0	0	0	1 (1)
Ecchymosis	0	0	1 (1)	0	0	0	1 (1)
Haematochezia	1 (1)	0	0	0	0	0	1 (1)
Haematoma	1 (1)	0	0	0	0	0	1 (1)
Haematuria	1 (1)	1 (1)	0	0	0	0	1 (1)
Haemoptysis	1 (1)	0	0	0	0	0	1 (1)
Haemorrhage	0	1 (1)	0	0	0	0	1 (1)
Menorrhagia	0	1 (1)	0	0	0	0	1 (1)
Periorbital haematoma	1 (1)	0	0	0	0	0	1 (1)
Purpura	0	1 (1)	0	0	0	0	1 (1)
Rectal haemorrhage	1 (1)	0	0	0	0	0	1 (1)
Thrombotic thrombocytopenic purpura	0	0	1 (1)	0	0	0	1 (1)
Vaginal haemorrhage	0	0	1 (1)	0	0	0	1 (1)

Source: Dynamic Data Listings 19OCT2018
NR, not related; R, Related

2 STUDY OBJECTIVES

2.1 Phase 1a Dose Escalation

The primary objective of the escalation phase of the study is to characterize the safety profile and DLT of TTI-621 in order to identify the MTD and/or the optimal dose in adult subjects with advanced relapsed or refractory lymphomas.

Secondary objectives include characterization of the PK of TTI-621, development of ADA, and pharmacodynamics (PD) through various biomarker studies.

2.2 Phase 1b Dose Expansion (Part 2 and Part 3)

The primary objective of the expansion phase of the study is to further characterize the safety of TTI-621 in an expanded number of primary hematologic malignancies and selected solid tumors, and to evaluate the safety of individual subject TTI-621 dose intensification.

Secondary objectives include additional characterization of PK, PD, and development of ADA; and to gain preliminary evidence of the anti-tumor activity of TTI-621 in subjects with a variety of hematologic malignancies and selected solid tumors. In addition, the safety of TTI-621 will be evaluated in combination with other anti-cancer agents.

2.3 Phase 1b Dose Expansion (Dosing Optimization, Part 4)

The primary objective of the dose optimization phase is to further evaluate the safety and tolerability of TTI-621 at dose levels higher than the initially recommended phase 1b dose of 0.2 mg/kg (as determined during phase 1a dose escalation) and the MTD and/or recommended phase 2 dose will be re-assessed per revised DLT criteria following a 3+3 dose escalation schema. The DLT criteria are revised based on the totality of safety data collected thus far from the phase 1a and 1b dose expansion phase of the study. The starting dose for this further dose evaluation will be the highest dose of TTI-621 evaluated (0.5 mg/kg) during phase 1b dose expansion following dose intensification regimens permissible per protocol (Part 2 and Part 3).

Secondary objectives include characterization of the PK, PD, immunogenicity, and preliminary evidence of antitumor activity of TTI-621 in patients with relapsed and/or refractory CTCL at higher dose levels of TTI-621.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

Study TTI-621-01 is a multicenter, open-label, phase 1a/1b trial of TTI-621 in subjects with relapsed or refractory hematologic malignancies and selected solid tumors; the study will be conducted in 4 parts.

Part 1: In the dose escalation phase, subjects with advanced relapsed or refractory lymphomas will be enrolled in sequential cohorts to receive escalating dose levels of TTI-621 as outlined in Table 3-1 for the purpose of characterizing safety, tolerability, and identifying the MTD and/or the optimal dose.

Part 2: In the expansion phase, Part 2, subjects with a broader variety of hematologic malignancies and selected solid tumors will be treated at a TTI-621 dose based on the putative optimal dose in order to further define safety, characterize the efficacy, and evaluate the safety of individual subject TTI-621 dose intensification. A cohort of subjects with CD20-positive malignancies will also be enrolled and treated with TTI-621 plus rituximab to characterize the safety and efficacy of the combination. Similarly, a cohort of subjects with classic HL (cHL) will be treated with TTI-621 plus nivolumab to characterize the safety and efficacy of the combination. The phases of the study are described in more detail below.

Part 3: In the expansion phase, Part 3, based upon preliminary observations of response, 2 cohorts (subjects with CTCL and PTCL), will be evaluated separately, using the Simon 2-stage design, for the potential to be further studied.

As of November 1, 2016, the MTD/optimal dose for TTI-621 monotherapy was determined by the SRC to be 0.2 mg/kg. The starting dose of TTI-621 to be administered in combination with other agents is 0.1 mg/kg (see Section 1.8 for details of DLTs and cohort advancement and Section 6.4 for further dosing information). In vitro studies suggest that increased CD47 receptor occupancy by TTI-621 is associated with increased macrophage-mediated phagocytosis of tumor cells. The observation that the degree of thrombocytopenia has been attenuated with subsequent doses for many subjects who were not platelet transfusion-dependent suggests compensatory increases in marrow platelet production that may enable safe intrasubject dose intensification. Therefore, under phase 1b Part 3 dose intensification will be required for all newly enrolled subjects starting at Week 3, in 0.1 mg/kg weekly increments, to a maximum of 0.5 mg/kg/week (see Section 6.5.4 for details).

Part 4: In the dose optimization phase, Part 4, the safety and tolerability of TTI-621 at higher dose levels beyond the initially recommended phase 1b dose of 0.2 mg/kg (as

determined during phase 1a dose escalation) and the highest dose of TTI-621 evaluated (0.5 mg/kg) during phase 1b dose expansion following dose intensification permissible per protocol, will be evaluated. This phase 1b dose optimization phase will aim at re-defining MTD and/or recommended phase 2 dose following 3+3 dose escalation schema and a revised DLT criteria based on the totality of safety data collected thus far from phase 1a and 1b dose expansion phase of the study.

The major revision to the DLT criteria as used in phase 1a relates to Grade 4 thrombocytopenia. The safety data collected thus far from phase 1a and ongoing phase 1b expansion (by data cut-off of 01 October, 2018) showed that ≥ Grade 3 related thrombocytopenia and platelet count decrease occurred in 11% and 9% of patients respectively. Thrombocytopenia appeared to be transient and in general recovered within a week prior to the next dosing. Thrombocytopenia was not found to be associated with increased incidence of bleeding and had limited impact on the study drug delivery. Based on the data, Grade 4 thrombocytopenia will be revised to qualify as a DLT only when the event lasts longer than 72 hours. Subject data obtained from the phase 1b Part 3 CTCL and PTCL cohorts stage 1 will be evaluated per Simon 2-stage criteria previously established.

In phase 1b dose optimization of the study (Part 4), further dose escalation of TTI-621 will be pursued in patients with relapsed and/or refractory CTCL following a 3+3 escalation design and using a revised DLT criteria. Dose optimization will proceed following review of the data obtained from the phase 1b Part 3, stage 1 cohorts of CTCL and PTCL subjects.

3.2 Phase 1a Escalation (Completed)

3.2.1 Dose Advancement and MTD Determination

A minimum of 3 subjects will be treated in each dose cohort in a conventional 3 + 3 design (Table 3-1) starting at Cohort 1. Given the potential risk for cytokine release syndrome, the first subject in each dosing cohort will be treated and observed for 72 hours before the next subject can receive their first infusion of TTI-621. Cohort 0 represents a contingency de-escalation dose level in the event that tolerance issues are encountered in Cohort 1. Treatment for an individual subject is described in Section 6.3.

Table 3-1: TTI-621 Dose Levels by Cohort

Cohort	N	Dose (once weekly)
0	3 (+ 3)	0.01 mg/kg
1	3 (+ 3)	0.05 mg/kg
2	3 (+ 3)	0.1 mg/kg
3	3 (+ 3)	0.3 mg/kg
4	3 (+ 3)	1 mg/kg
5	3 (+ 3)	3 mg/kg
6	3 (+ 3)	10 mg/kg

Subjects will receive TTI-621 at the assigned dose once weekly for a planned 3 weeks of treatment/observation for DLT assessment. In the absence of DLT (as defined in Section 3.2.2) in 3 evaluable subjects within a cohort, dose advancement will proceed through the successive cohorts. All subjects in each dose cohort must have completed the DLT observation period before the next dose cohort commences treatment.

Subjects will be considered evaluable for DLT if they received all 3 weekly doses within the specified treatment/observation period or if they experienced an AE meeting the criteria for DLT during that time. Those who drop out of the study during the first 3 weeks for reasons other than toxicity or who experience a delay in dosing of more than 3 days for reasons other than DLT are considered unevaluable for DLT and will be replaced with a new subject enrollment. For subjects who experienced a treatment delay, the DLT observation period will extend 7 days beyond the third dose of TTI-621.

If DLT as defined below is encountered in 1 subject within a particular dose cohort, additional subjects will be treated in that cohort as outlined in Table 3-2. Based on the incidence of DLT, the MTD will be determined. Depending upon the tolerance at a particular dose level, intermediate dose levels may be studied to more closely characterize DLT and more accurately identify the MTD as recommended by the Safety Review Committee (SRC).

Table 3-2: Dose Escalation Rules

If DLT was observed in:	Then:
0 of 3 subjects	Proceed with enrollment in next cohort
1 of 3 subjects	Enroll 3 additional subjects in current cohort
1 of 6 subjects	Proceed with enrollment in next cohort
≥ 2 of 6 subjects	Do not escalate; enroll 3 additional subjects in previous cohort or new intermediate dose level
≥ 2 of 3 subjects	Do not escalate; enroll 3 additional subjects in previous cohort or new intermediate dose level

Individual subjects may continue receiving additional TTI-621 treatment until disease progression, unacceptable toxicity, or other reason for treatment discontinuation. As of Protocol Amendment 6, intrasubject dose escalation may be employed for active subjects in the dose-escalation phase of the study (see Section 1.8.3).

3.2.2 Definition of Maximum Tolerated Dose

The MTD is defined as the dose level immediately below that in which 2 or more of either 3 or 6 subjects experienced DLT during the first 3 weeks of treatment. At least 6 subjects must be treated at the putative MTD, with no more than 1 incident of DLT. AEs that manifest after the 3-week DLT observation period or cumulative toxicities will be considered in the final definition of MTD.

The final determination of the optimal dose for further use in the expansion phase may or may not be synonymous with the MTD but will consider both acute and cumulative toxicities; the incidence of required dose delays, reductions, and discontinuations; and the overall facility of administration in clinical practice.

3.3 Phase 1b Expansion

3.3.1 Phase 1b - Part 2 and Part 3

In Part 2 of the expansion phase of the study, the safety and preliminary anti-tumor activity of TTI-621 monotherapy at the optimal dose identified in the escalation phase will be explored in 12–15 subjects per cohort type, as outlined in Table 3-3 below. These cohorts include: indolent B-cell lymphomas (IBCL; see Appendix A), aggressive B-cell lymphomas (ABCL; see Appendix A), T-cell lymphoma (TCL), HL,

CLL, ALL, multiple myeloma (MM), AML, MDS, myeloproliferative neoplasms (MPN), and SCLC. A cohort of subjects with CD20-positive malignancies will also be enrolled and treated with TTI-621 in combination with rituximab. Similarly, a cohort of subjects with cHL will be treated with TTI-621 plus nivolumab. If preliminary evidence of clinical benefit is observed in association with acceptable tolerability, one or more hematologic disease-specific cohorts may be expanded to a maximum of 40 subjects (see Section 8.3 for details). In the rare instance that a subject has more than one malignancy, the subject will be assigned to a single cohort based upon the Investigator's assessment of the subject's greatest clinical need.

In Part 3 of the expansion phase of the study, the safety and preliminary anti-tumor activity of TTI-621 monotherapy will be further explored in two cohorts of CTCL and PTCL subjects ((consisting of T- and NK-cell neoplasms per WHO definition (Swerdlow et al., 2016)), starting with the optimal dose identified in the escalation phase. Dose intensification to a maximum of 0.5 mg/kg/week will be required for all newly enrolled subjects per Section 6.5.4, following a ramp-up schedule (2 weeks of study treatment at 0.2 mg/kg followed by dose intensification between week 3 and week 8 at increments of 0.1 mg/kg/week as tolerated up to maximum dose of 0.5 mg/kg/week). The overall response in each of the 2 cohorts (CTCL and PTCL) will be evaluated separately using the Simon 2-stage design.

As of Protocol Amendment 9, enrollment will be limited to the following disease types: CD20+ NHL (in combination with rituximab), cHL (in combination with nivolumab), CTCL and PTCL.

Treatment may continue until evidence of unequivocal disease progression is seen (see Section 7.14.1), unacceptable toxicity, or other reason for treatment discontinuation. For patients who have been given weekly infusion of TTI-621 for more than a year and are receiving clinical benefit (objective response or clinically meaningful long-term stable disease), investigators may exercise their discretion to reduce the d osing frequency from weekly to bi-weekly following the discussion and approval from the sponsor or designees.

An overview of monotherapy and combination treatments administered in the expansion phase is provided in Table 3-3. Starting doses of TTI-621 are shown; intrasubject dose-intensification is required as outlined in Section 6.5.4.

Table 3-3: Disease Cohorts and Schedule of Treatments Administered in the Expansion Phase Part 2 and Part 3

	Expansion Cohort	TTI-621 Starting Dose (mg/kg/wk)	Combination Partner Dose
Monotherapy	IBCL (closed)	0.2	NA
	ABCL (closed)	0.2	NA
	TCL (closed)	0.2	NA
	CTCL	0.2	NA
	PTCL	0.2	NA
	HL (closed)	0.2	NA
	CLL (closed)	0.2	NA
	ALL (closed)	0.2	NA
	MM (closed)	0.2	NA
	AML (closed)	0.2	NA
	MDS (closed)	0.2	NA
	MPN (closed)	0.2	NA
	SCLC (closed)	0.2	NA
Combination Therapy	Rituximab combination: CD20-positive malignancy	0.1	375 mg/m^2/wk for up to 8 cycles[a]
	Nivolumab combination: cHL	0.1	per FDA approved package insert for cHL[b]

NA: not applicable
[a] Subjects may continue on TTI-621 monotherapy upon completion of combination partner regimen/unacceptable toxicity to the combination regimen
[b] Subjects who have unacceptable toxicity to the combination regimen may continue to receive TTI-621 monotherapy

3.3.2 Phase 1b Dose Optimization Part 4 (to be enrolled as of Amendment 9)

A minimum of 3 patients will be treated in each cohort sequentially in a 3 + 3 design. The planned dose escalation levels are shown in Table 3-4. Patients will receive once weekly dosing of TTI-621 at the dose levels in their assigned cohort regimen (Week 1 given on Day 1, Week 2 given on Day 8, and Week 3 given on Day 15). The DLT observation period is 21 days. Patients will be considered evaluable for DLT if they receive all 3 weekly doses within the DLT evaluation period or if they experience an AE meeting DLT criteria during that time. If a patient experiences a non-DLT event that requires a dose to be held per dose modification guideline (Section 6.5), the DLT evaluation period can be extended to 28 days. If a DLT occurs in 1 of 3 patients within a cohort, 3 additional patients will be treated at that cohort regimen. In the absence of DLT, enrollment will proceed sequentially through the planned dose levels.

Alternative dose escalation including evaluation of intermediate doses, expansion of an existing dose level, evaluation of alternative regimens/schedules including a dose ramp-up design following different dose intensification increments and schedule, and modification of dosing frequency and/or IV infusion rate are all permissible if supported by the evolving data and a SRC decision. All patients in each cohort must have completed the 21-day DLT period before the next cohort begins treatment. The MTD of TTI-621 will be the dose below the one in which ≥2 DLTs are observed among 6 treated patients.

Table 3-4: Planned Dose Escalation Levels

		TTI-621 dose (mg/kg) DLT evaluation period		
Level	**N**	**Week 1[b]**	**Week 2**	**Week 3**
0	3 (+ 3)	0.2	0.5	0.5
1[a]	3 (+ 3)	0.5	0.5	0.5
2	3 (+ 3)	0.7	0.7	0.7
3	3 (+ 3)	1.0	1.0	1.0
4	3 (+ 3)	1.4	1.4	1.4

[a] Level 1 = starting dose

[b] If de-escalation to level 0 is required, all subsequent cohorts will start with a priming dose of 0.2 mg/kg at week 1 followed by the respective dose level escalation increments (0.7, 1.0, 1.4 mg/kg) at week 2 or subsequent weeks, as applicable, based on SRC decision.

In the starting dose level (0.5 mg/kg), the first 3 patients will be treated sequentially to allow close monitoring of toxicity and timely dose adjustment if needed. The third patient will not start the study treatment until the first and second patient, respectively, have completed the initial two weeks of study treatment and had no observation of TEAEs meeting DLT criteria. If the first or second patient experiences a DLT event within the first two weeks of treatment, de-escalation to Level 0, a priming dosing regimen, will be considered per SRC discussion and decision. A priming regimen refers to a dosing regimen that involves a lower priming dose used during the initial week(s) of treatment followed by further dose escalation to a higher and stable dose for continued use throughout the course of the study. At Level 0, patients will be dosed at 0.2 mg/kg for the first week and then receive a stable dose of 0.5 mg/kg for the remainder of the study.

If Level 0 is determined to be tolerable per 3+3 schema, further escalation of doses beyond 0.5 mg/kg in Week 2 and beyond will be considered, as part of the priming dosing regimen. The same dose escalation increment (to 0.7, 1, and 1.4 mg/kg) may be followed after the initial week of exposure to 0.2 mg/kg.

The MTD is defined as the dose level immediately below the lowest dose that at which 2 or more of either 3 or 6 patients experienced a DLT during the 3-week DLT period. At least 6 patients must be treated at the putative MTD, with no more than 1 incidence of DLT. AEs that occur after the 3-week DLT period or cumulative toxicities will be considered in the final designation of MTD.

If MTD is not reached after completion of all planned dose escalation levels, a decision will be made in consultation with the SRC (see Section 3.4), to either continue further escalation at a maximal 50% escalation increment, or d ose escalation will be halted. A maximum assessed dose (MAD) could be used in lieu of the MTD. The SRC will review the totality of the safety, tolerability, PK, PD, and preliminary efficacy data (if available) before making this decision.

In addition to MTD/MAD determination, SRC will review the totality of cumulative toxicity and tolerability data in balance against the PK, PD and preliminary efficacy data. If a biologically active dose appears to be lower than MTD/MAD or if the MTD/MAD results in dose modification due to tolerability that limits continued dose exposure and in turn compromise the potential efficacy gain, a recommended phase 2 dose of TTI-621 lower than MTD/MAD can be determined for future single agent studies. Minimally 6 patients will need to be evaluated at the recommended phase 2 dose before formal designation.

After MTD/MAD or recommended phase 2 dose (if different from MTD/MAD) is determined, an additional 6 patients will be enrolled and treated at this dose level to form a safety expansion cohort of a total of 12 patients (including the 6 patients treated at the designated phase 2 dose before the dose selection). Preliminary efficacy will also evaluated in this cohort of patients.

3.3.3 Definition of Dose-limiting Criteria for Phase 1b Part 4 (Amendment 9)

Dose-limiting toxicity is defined as any of the following TEAEs that occur during the 21-day DLT treatment/observation period (including the pre-dose tests on Day 22/Week 4 Day 1) and that are considered at least possibly related to study treatment by the investigator. Note that any AEs for which the relationship to study treatment cannot be ruled out should be considered possibly related:

Hematologic toxicity

- Grade 4 thrombocytopenia ($<25 \times 10^9$/L) lasting >72 hours or a platelet count $\leq 10 \times 10^9$/L at any time

- ≥ Grade 3 thrombocytopenia with bleeding (except epistaxis or gingival bleeding that is less than 24 hours in duration and does not require medical intervention, or normal menses) or requiring platelet transfusions
- Grade 4 anemia, unexplained by underlying disease
- Grade 4 neutropenia lasting >72 hours
- Grade 3 febrile neutropenia lasting >72 hours
- Grade 4 febrile neutropenia

Non-hematologic toxicity

- Grade 3 or higher non-hematologic toxicity with the following exceptions:
  - Grade 3 nausea and/or vomiting lasting <72 hours with standard supportive care
  - Transient Grade 3 fatigue lasting ≤72 hours
  - Transient asymptomatic Grade 3 laboratory abnormalities considered not clinically significant following agreement between investigators and the sponsor's medical monitor and that last <72 hours with standard supportive care
- Other ≥ Grade 2 TTI-621-related non-hematologic toxicities that, in the opinion of the investigator, require a dose reduction or discontinuation of TTI-621

3.4 Safety Review Committee

A SRC oversees the safety of all phases of the study. During the phase 1b dose optimization (Part 4) of the study, the SRC convenes at appropriate intervals (when all 3 or 6 subjects in a given cohort are evaluable for DLT determination) to review all available safety data in a cohort, cumulative information from all dosed subjects, and any new preclinical information, as in phase 1a. The SRC renders decisions on dose escalation and other safety aspects of the study. All actions of the SRC are documented in written minutes.

During phase 1b dose optimization (Part 2 and Part 3), any significant safety and tolerability issues observed based on medical monitoring and pharmacovigilance signal detection can be discussed at SRC for recommendation on any actions taken. The SRC can also convene to discuss any individual patient cases brought forth for advice by the treating investigators or the sponsor. The SRC will extend its responsibility under Amendment 9 to review both safety and efficacy data to recommend a decision as to whether or when to proceed with the Part 3 CTCL and PTCL cohorts to next stage per the Simon's 2-stage design in parallel to the Part 4 dose optimization phase of the study. The membership of the SRC may vary between different phases of the study and will be documented in the SRC Safety Committee Charter.

During phase 1a, the SRC consisted of the Chief Medical Officer/Medical Monitor, Head of Clinical Operations, all enrolling Investigators, and other Sponsor personnel as appropriate. Under Amendment 9, the SRC will involve all enrolling investigators in the data review and discussion but due to the size of the participating sites, only selected 3-5 investigators will function as the official members of the SRC and will therefore have the voting right. All discussions and decisions of the SRC will be documented in writing.

3.5 Number of Subjects

The dose escalation portion of the study is estimated to enroll up to 36 subjects with an advanced lymphoma. The dose expansion phase 1b (Part2) will enroll 12–15 subjects per cohort type. If preliminary evidence of clinical benefit is observed in association with acceptable tolerability, one or more hematologic disease-specific cohorts may be expanded up to a maximum of 40 subjects. For the dose expansion phase 1b (Part 3), the number of subjects in the CTCL and PTCL cohorts will be enrolled based upon a Simon optimal 2-stage design with a maximum of 35 subjects in each cohort.

In addition, approximately 25 subjects will be enrolled for the phase 1b dose optimization (Part 4). The total number of subjects enrolled in the study is approximately 285 subjects (see Section 8.3 for details).

3.6 Investigational Sites

Approximately 20 institutions will enroll subjects into this study.

3.7 Study Duration

The dose-escalation phase of the study is expected to run for approximately 18 months and the expansion phase of the study for approximately 5 years.

4 SELECTION OF STUDY POPULATION

Potential subjects must sign an informed consent form before any study-specific screening tests may be conducted. Screening tests are described in Section 7.1.

4.1 Inclusion Criteria

Phase 1a Escalation (Completed and now Closed)

1. Histologically documented, advanced lymphoma after the failure of at least 2 prior therapies with at least one site of measurable disease (≥ 1.5 cm in the long axis or ≥ 1.0 cm in both the long and short axis). Additionally, subjects with NHL (indolent and aggressive B-cell lymphomas) should have failed CD20-targeted therapy.

2. Adequate hematologic status (in the absence of transfusion and growth factor support for at least 28 days), defined as:
    - absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    - platelets ≥ 75 x 10^9/L
    - hemoglobin ≥ 10 g/dL

Phase 1b Expansion (Selected Cohorts Currently Open for Parts 2 and 3)

1. Advanced measurable malignancy documented by histology, cytology, flow cytometry, fluorescent in situ hybridization (FISH) or polymerase chain reaction (PCR) methodology in one of the following categories:
    - (closed) Small cell lung cancer (SCLC) (measurable disease by the Response Evaluation Criteria in Solid Tumors [RECIST], Version 1.1)
    - Histologically documented, advanced lymphoma after the failure of at least 2 prior systemic therapies with at least one site of measurable disease (≥ 1.5 cm in the long axis or ≥ 1.0 cm in both the long and short axis). Additionally, subjects with CD20-positive NHL (indolent and aggressive B-cell lymphomas) should have failed CD20-targeted therapy
        - Indolent B-cell lymphoma (see Appendix A)
        - Aggressive B-cell lymphoma (see Appendix A)
        - Classic Hodgkin lymphoma
            - Patients with cHL should have failed at least one checkpoint inhibitor therapy before enrolling to the nivolumab combination cohort
    - Peripheral T-cell lymphoma ([PTCL] as defined by mature T- and NK-cell neoplasms per WHO and CTCL, see Appendix A), having failed at least 1 prior systemic therapy. Subjects with PTCL must have at least

1 site of measurable disease (≥ 1.5 cm in the long axis or ≥ 1.0 cm in both the long and short axis)

- CTCL (both MF and SS):
  - Failed at least 2 prior systemic therapies for CTCL. Systemic therapy does not include local radiation therapy or topical agents
  - Malignancy is measurable per global CTCL criteria (Olsen, 2011)
  - History of histologically-documented diagnosis of CTCL stage IIB to IVB (Olsen, 2011)
- (closed) B-cell or T-cell acute lymphoblastic leukemia (ALL):
  - First or greater bone marrow relapse from complete remission, or
  - Any bone marrow relapse after allogeneic transplant, or
  - Absence of complete remission after 2 induction attempts employing standard regimens, or
  - Ph+ B-ALL if subjects are intolerant to or ineligible to receive tyrosine kinase inhibitor therapy or have progressed after at least one line of this therapy
- (closed) CLL: subjects should have failed at least 2 prior therapies, including CD20-targeted therapy
- (closed) Multiple myeloma (MM): subjects should have failed at least 3 prior therapies, including an immunomodulatory drug (IMID) and proteasome inhibitor-based therapy and have measurable disease as defined as 1 or more of the following:
  - serum M-protein > 0.5g/dl and/or
  - urine M-protein > 200 mg/24 hours and/or
  - in subjects who do not meet these criteria, serum free light chains (FLC) > 100 mg/L (involved light chain) and abnormal ratio (FLC kappa/FLC lambda)
  - biopsy-proven plasmacytoma
- (closed) AML, with the exception of AML M3 using the French American British (FAB) classification (i.e., acute promyelocytic leukemia [APL]):
- (closed) MDS of WHO classifications RAEB-1 (refractory anemia with excess blasts) and RAEB-2
- (closed) BCR/ABL1-negative myeloproliferative neoplasm (MPN) or myeloproliferative/myelodysplastic overlap neoplasm (MPN/MDS) per the revised 2016 WHO criteria, including:
  - chronic phase (CP) (defined as peripheral blood and bone marrow <10% blasts) primary myelofibrosis or post-essential

thrombocythemia (post-ET) or post-polycythemia vera (post-PV) myelofibrosis

- if the diagnosis is Myelofibrosis-CP, must have Dynamic International Prognostic Scoring System (DIPSS) intermediate-2/high risk disease (Passamonti et al., 2010) and either be: 1) intolerant/resistant to ruxolitinib or 2) ineligible for ruxolitinib therapy, as determined by the treating Investigator

- accelerated phase/blast phase MPN (MPN-AP/BP) (defined as either a peripheral blood or bone marrow with ≥10% blasts)
  - if the diagnosis is MPN-AP/BP, must have progressive/resistant disease after treatment with a DNA methyl transferase 1 (DNMT1) inhibitor therapy (e.g. azacitidine or decitabine), as determined by the treating Investigator
- chronic myelomonocytic leukemia (CMML) -1 or 2 characterized by
  - >1x10^9/L monocytes and 2-19% blasts in peripheral blood or Auer rods and
  - dysplasia in ≥ 1hematopoietic line and 5-19% marrow blasts or Auer rods

- (closed) Subjects with MPN or MPN/MDS must not be eligible to proceed with hematopoietic stem cell transplantation (HSCT) and must have:
  - for MPN, an indication to treat with cytoreductive drugs (e.g. hydroxyurea, anagrelide, interferon, ruxolutinib, etc.), according to the judgment of the treating physician
  - for MPN, documentation of inadequate response or intolerance to first line therapy, which includes at least one cytoreductive drug (e.g. hydroxyurea, anagrelide, interferon, ruxolutinib, etc.)
  - for CMML, documentation of inadequate response or intolerance to first line therapy, which includes at least one hypomethylating agent

2. Hematologic status as follows (transfusions not permissible to achieve these levels within 14 days prior to the first dosing of study drug):
   - ANC ≥ 1 x 10^9/L (not applicable to subjects with AML, ALL, MDS, or MPN/MDS)
   - platelets ≥ 75 x 10^9/L (≥50 x 10^9/L if the patient has bone marrow involvement)
   - hemoglobin ≥ 9 g/dL

Phase 1b Expansion (Dose Optimization Part 4)

1. Histologically confirmed diagnosis of CTCL (both Mycosis Fungoides and Sezary Syndrome):
    - Failed at least 2 prior systemic therapies for CTCL (systemic therapy does not include local radiation therapy or topical agents)
    - Malignancy is measurable per global CTCL criteria (Olsen, 2011)
    - History of histologically-documented diagnosis of CTCL stage IB to IVB (Olsen, 2011)

3. Hematologic status as follows (transfusions not permissible to achieve these levels within 14 days prior to the first dosing of study drug):
    - ANC $\geq 1 \times 10^9$/L
    - platelets $\geq 75 \times 10^9$/L
    - hemoglobin ≥ 9 g/dL

Both Phases

1. Male or female 18 years of age or older

2. Availability of fresh or archived tumor tissue for immunohistochemical studies. Archival tissue may be used provided it was obtained subsequent to the last prior anti-cancer therapy. For subjects with SS, peripheral blood is acceptable.

3. Relapsed or refractory disease that has previously progressed on, or is currently progressing on standard anticancer therapy or for whom no other approved conventional therapy exists

4. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (see Appendix B)

5. Adequate coagulation function, defined as:
    - International Normalized Ratio (INR) < 1.5 x the upper limit of normal (ULN) for that laboratory
    - partial thromboplastin time < 1.5 x ULN
    - subjects receiving anticoagulation therapy must be on a stable dose with monitoring studies within therapeutic range per local institutional standards
6. Adequate hepatic function, defined as:

- total bilirubin < 1.5 x ULN unless considered due to Gilbert's disease
- alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 1.5 x ULN or < 3 x ULN with documented liver metastases

7. Adequate renal function, defined as estimated serum creatinine clearance > 30 mL/minute calculated using the Cockcroft-Gault equation (see Appendix E).

8. Recovery from the toxicities of previous anticancer drugs or radiotherapy to Grade 0 or 1 (or to baseline grade if condition was pre-existing)

9. Commitment from male and female subjects of reproductive potential to use, from the time of screening through 60 days after the last dose of TTI-621, either:

   - one highly effective method of contraception, including hormonal contraceptives (e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants), intrauterine device (IUD) or intrauterine system (IUS), vasectomy, or tubal ligation

   OR

   - at least 2 effective methods of contraception, including male condom, female condom, cervical cap, diaphragm, or contraceptive sponge

   OR

   - abstain from sex during study participation and for 60 days after the last dose of TTI-621

4.2 Exclusion Criteria

Both Phases

1. (AML cohort closed) AML M3 by FAB classification (APL)

2. Known, current central nervous system disease involvement or untreated brain metastases

3. Investigational agent or any anticancer drug within 14 days prior to planned start of treatment (with the exception of hydroxyurea in subjects with MPN, MPN/MDS, ALL or AML; see Section 6.8.2)

4. Allogeneic transplant within 30 days prior to the planned start of treatment or subjects with active graft-vs-host disease with the exception of Grade 1 skin involvement (see Appendix C)

5. Prior anti-CD47 therapy, with the exception of prior TTI-621 therapy delivered intratumorally only

6. Major surgery within 28 days prior to planned start of treatment

7. Use of irreversible antiplatelet/anticoagulant agents within 7 days prior to planned start of treatment (except subjects with thrombocytosis where low dose aspirin is being used to reduce the risk of thrombosis); use of low dose aspirin (≤81 mg/day) and selected, reversible anticoagulants are permitted (low molecular weight heparin, heparin, warfarin and dabigatran)

8. History of hemolytic anemia or bleeding diathesis

9. Uncontrolled infection requiring systemic antibiotics/antivirals/antifungals

10. Chronic use of systemic corticosteroids of more than 20 mg per day of prednisone or equivalent; enrollment of post-transplant subjects who are on corticosteroids for graft-vs-host disease prophylaxis requires approval of the Medical Monitor. CTCL patients who are on a stable dose of medium or low potency topical corticosteroids for at least 4 weeks prior to study entry may continue its use on study at the same dose.

11. Known hypersensitivity to any component of study drug

12. Positive serum pregnancy test in females of child-bearing potential or current breastfeeding

13. Significant cardiovascular disease such as symptomatic congestive heart failure (New York Heart Association Class III or IV), symptomatic coronary artery disease, myocardial infarction within the last 6 months, unstable arrhythmia requiring treatment, unstable angina, or prolonged QTc interval > 480 milliseconds (Grade 2 or higher) (QTc interval calculation at the discretion of the Investigator)

14. Active hepatitis B or C or a history of HIV infection

15. Other significant medical condition unrelated to the primary malignancy that would compromise subject's safety or ability to comply with protocol requirements

16. Inability for the subject to complete protocol requirements, such as geographic considerations, psychiatric disorders, or other compliance concerns

17. Prior Grade 4 rituximab infusion-related reaction (rituximab combination arm only)

18. Active autoimmune disease or history of autoimmune disease that might recur (nivolumab combination arm only); subjects with vitiligo or type I diabetes mellitus or residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement are permitted to enroll

5 ENROLLMENT PROCEDURES

At the time a prospective subject signs the informed consent form, a unique subject number will be assigned and Part 1 of the Registration/Enrollment Form completed and sent to the Sponsor or designee. Subjects will be screened for eligibility according to the criteria outlined in Section **Error! Reference source not found.**.

Phase 1b Dose Expansion Phase (Part 2 and 3)
Once a subject is deemed eligible, Part 3 of the Registration/Enrollment Form will be completed and sent to the Sponsor or designee.

Phase 1b Dose Optimization Phase (Part 4)
Once a subject is deemed eligible, Part 3 of the Registration/Enrollment Form will be completed and sent to the Sponsor or designee, at which time the TTI-621 dose level will be assigned. Additional instructions may be found in the separate Study Manual.

6 TREATMENT PROCEDURES

6.1 Investigational Product

TTI-621 is formulated as a sterile, clear, preservative-free liquid concentrate in 10 mM sodium phosphate, 150 mM sodium chloride, and water for injection, with pH adjusted to 7.4. Formulated TTI-621 is supplied in single-use vials containing 5.0 mL solution at a concentration of 10 mg/mL. TTI-621 may be stored at –20°C or colder and should be protected from light in a secure storage facility with limited access.

Additional information on the drug product may be found in the Investigator's Brochure; accountability instructions are in the Pharmacy Manual.

6.2 Method of Assigning Subjects to Treatment Groups

Subjects in the escalation phase of the study will be sequentially assigned to TTI-621 dose cohorts at the time of enrollment as described in Section 3.2.1. For the expansion phase of the study, subjects will receive treatment based on the dose selected from the escalation phase, unless otherwise specified (see Section 3.3).

6.3 Treatments Administered (All Phases)

6.3.1 Dosing Instructions

General
Premedication with an antihistamine and acetaminophen is required for all subjects prior to infusion of TTI-621.

TTI-621 will be thawed at room temperature and the required dose diluted into 250 mL of 0.9% sodium chloride for injection USP as further described in the Pharmacy Manual. If not used immediately, the prepared infusate may be stored as described in the Pharmacy Manual. The assigned dose of TTI-621 will be administered IV over 60 minutes (see Section 6.4.1 for expansion phase instructions). The start of the infusion (Time 0) is defined as after priming, immediately before commencement of the infusion. End of infusion is defined as the time immediately after the flush.

Vital signs will be monitored as outlined in Section 7.

The individual dose is determined based on the subject's current body weight. Body weight can be rounded per institutional procedures when calculating doses. Body weight will be taken weekly through Week 8, then every other week (Weeks 10, 12, etc.) After Week 8, the weight taken at the prior visit may be used to calculate dose (e.g. weight at Week 8 used for Week 9 dosing).

Each subject will receive TTI-621 in accordance with the assigned dose until disease progression, unacceptable toxicity, or other reasons for treatment discontinuation occur. For patients who have been given weekly infusion of TTI-621 for more than a year and are receiving clinical benefit (objective response or clinically meaningful long-term stable disease), investigators may exercise their discretion to reduce the dosing frequency from weekly to bi-weekly following the discussion and approval from the sponsor or designees. In the context of treatment discontinuation, unacceptable toxicity will include any Grade 4 TTI-621-related nonhematologic toxicity or a TTI-621-related toxicity that requires a dose delay of more than 3 weeks.

In the absence of disease progression, subsequent TTI-621 doses may be delivered based upon subject's clinical status with dose modifications per Section 6.5.

6.4 Treatments Administered – Expansion Phase

An overview of treatments administered for the monotherapy and combination therapy cohorts for Part 2 and Part 3, is provided in Table 3-3. Additional details are provided in the sections below.

6.4.1 TTI-621 Monotherapy

Phase 1b – Part 2 and Part 3

Subjects enrolled in these cohorts will receive a starting dose of 0.2 mg/kg/week TTI-621. For Part 3, intrasubject TTI-621 dose-intensification is required for newly enrolled subjects. All subjects will receive a dose ramp-up regimen which includes initial two-weeks of 0.2 mg/kg treatment followed by intrasubject dose intensification at an increment of 0.1 mg/kg per week up to 0.5 mg/kg within 5-8 weeks. Details regarding when dose intensification should be delayed or stopped due to AEs are provided in Section 6.5.3.

Phase 1b Dose Optimization - Part 4

Subjects in the phase 1b dose optimization phase (Part 4) will undergo dose escalation of TTI-621, starting with Level 1 (dose of 0.5 mg/kg) per dose escalation plan (See Table 3-4, Section 3.3.2) given once weekly. Following a 3+3 escalation design and using a revised DLT criteria, enrollment will continue through Level 2 (starting dose of 0.7 mg/kg), Level 3 (starting dose of 1.0 mg/kg) and Level 4 (starting dose of 1.4 mg/kg) respectively. In the starting dose cohort (0.5 mg/kg), the first 3 patients will be treated sequentially to allow close monitoring of toxicity and timely dose adjustment if needed. The second and third patient will not start the study treatment until the first and second patient, respectively, have completed the initial 2 weeks of study treatment and had no observation of TEAEs meeting DLT criteria. If a DLT is noted in Level 1, there may be de-escalation to Cohort 0 (priming dose of 0.2 mg/kg at week 1 followed by 0.5 mg/kg at subsequent doses) with progression through Levels 2, 3 and 4 using the dose priming approach of 0.2 mg/kg at week 1 followed by the respective level dose regimens at subsequent weeks.

6.4.2 TTI-621 plus Rituximab Combination Cohort

Subjects enrolled in this cohort will receive a starting dose of 0.1 mg/kg TTI-621 in combination with 375 mg/m^2 rituximab given weekly (1 cycle) for up to 8 cycles according to the institutional standard of care. Intrasubject TTI-621 dose-

intensification is required for newly enrolled subjects as outlined in Section 6.5.4. Subjects who complete 8 cycles of combination therapy or those who have unacceptable toxicity to the combination therapy prior to completion of 8 cycles may continue to receive TTI-621 as a single agent.

All subjects receiving the TTI-621 plus rituximab combination will have previously received rituximab and are thus less likely to experience the typical "first dose" infusion reactions upon re-exposure to rituximab. For subjects in this combination cohort, if rituximab is given on the same day as TTI-621, at least 60 minutes must elapse between completion of the rituximab infusion and initiation of the TTI-621 infusion. Rituximab may also be given the day before TTI-621 infusion, particularly for subjects who have a history of Grade 2 or 3 rituximab infusion-related reactions. Any rituximab infusion-related reactions must be Grade 2 or lower and have fully resolved to initiate the TTI-621 infusion on the same day. Any rituximab infusion-related reactions that do not meet these criteria must be discussed with the Medical Monitor to determine optimal next steps. Subjects who have had a prior Grade 4 rituximab infusion reaction will not be included in the combination TTI-621 plus rituximab cohort.

6.4.3 TTI-621 plus Nivolumab Combination Cohort

Subjects enrolled in this cohort will receive a starting dose of 0.1 mg/kg/week TTI-621 in combination with nivolumab at 3mg/kg given every 2 weeks or a fixed dose per current FDA approved package insert for cHL. Intrasubject TTI-621 dose-intensification is required for newly enrolled subjects as outlined in Section 6.5.4. Subjects who have unacceptable toxicity to nivolumab may continue to receive TTI-621 as a single agent.

For subjects in this combination cohort, if nivolumab is given on the same day as TTI-621, at least 60 minutes must elapse between completion of the nivolumab infusion and initiation of the TTI-621 infusion. Nivolumab may also be given the day before TTI-621 infusion. Any nivolumab infusion-related reactions must be Grade 2 or lower and have fully resolved to initiate the TTI-621 infusion on the same day. Any nivolumab infusion-related reactions that do not meet these criteria must be discussed with the Medical Monitor to determine optimal next steps.

6.5 Dose Modifications (Amendment 9)

This section below will be used for the entire phase 1b expansion phase per Amendment 9, including both part 2, part 3 and the dose optimization phase part 4, except where otherwise noted.

6.5.1 General Principles

Patients will be evaluated according to the Schedule of Assessments (See Appendix D. Table 1 and Appendix D. Table 2) for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI CTCAE version 4.03. All toxicities that occur during the study will be actively managed following the standard of care per local institutional practice unless otherwise specified in the protocol. The investigator should try to the best of his/her ability to assess whether an AE is related or possibly related to study drug, and dosing actions of TTI-621 will then be considered accordingly.

In general, patients who have the TTI-621 dose held due to treatment-related or possibly related AE may resume study drug after resolution of the AE, at the same dose level or at a reduced level (dose reduction) by at least 1 dose level. When a dose reduction occurs, the TTI-621 dose will be reduced to the next lower dose either by following the ramp-up dosing regimen in Part 3 or on the established safe dose during phase 1b dose optimization part 4. If the initial dose adjustment does not provide sufficient relief, the dose of TTI-621 can be further reduced if the investigator considers that the patient is benefiting from study treatment and may benefit at a further dose reduced dose level of TTI-621. When a dose reduction of TTI-621 is required due to toxicity, no dose re-escalation will be permitted. If TTI-621 dosing is delayed for > 21 days for TTI-621-related or possibly related toxicities despite supportive treatment per standard clinical practice or more than 2 dose reductions are required in a patient, the investigator should consider discontinuing the patient from study treatment, unless the investigator, after risk-benefit assessment, considers that the patient may benefit from continued study treatment after resolution of AEs and when the re-treatment criteria are satisfied per Section 6.5.2. The patient will continue to be followed for 30 days after the last administration of TTI-621.

Patients who experience a DLT (during DLT evaluation period) or a DLT-like toxicity within the first 21 days of treatment, generally, require that treatment with TTI-621 be permanently discontinued. The patient will be followed until resolution or stabilization of the event. The investigator and medical monitor will decide on a case-by-case basis if it is in the patients' best interest to continue the study treatment. If continuation of

treatment is in the patients' best interest, the dose of TTI-621 will be reduced by at least 1 dose level upon resumption of treatment following recovery of the toxicity or toxicities to a level that satisfies the retreatment criteria (see Section 6.5.2). The discussion and decision will be documented.

In managing toxicities, dose modification guidelines should be followed closely. However, based on the evolving safety data of TTI-621 and/or individual patient cases, alternative dose modifications may be recommended after discussion between the investigator and medical monitor to maximize exposure of study treatment while protecting patient safety. In principle, dose modification is only required per guidance as described below when the AE is determined to be related to the study drug. However, when non-study-drug related AEs, in the investigator's assessment, would likely result in a medical condition where continuous dosing would add unwanted physical burden and stress to the patient, temporarily withholding the study drug is allowed. Discussions between the investigator and medical monitor are highly encouraged in these instances.

6.5.2 Criteria for Retreatment and Dose Delays

TTI-621 is given as weekly infusions. Before each TTI-621 dose can be delivered, the patients' ANC must be $\geq$ 1 x10^9/L and the platelet count must be $\geq$ 75 x10^9/L or baseline. In addition, all other toxicity considered to be related to treatment with TTI-621 must have resolved to $\leq$Grade 1 or to the patient's baseline values with the exceptions listed below. If other AEs, not listed below, resolve to a level that is determined to be acceptable (and $\leq$Grade 2) for TTI-621, re-dosing is allowed based on a benefit-risk assessment by the investigator and medical monitor on a case by case basis. The decision will be documented.

Exceptions:

- Grade 2 gastrointestinal symptoms such as nausea, vomiting, and diarrhea that are easily treatable
- Grade 2 fatigue or other constitutional symptoms
- Grade 2 lymphopenia, neutropenia, and/or leukopenia in the absence of opportunistic infection
- Grade 2 thrombocytopenia in the absence of clinically meaningful bleeding
- Grade 2 anemia in the absence of shortness of breath and/or congestive heart failure
- Transient asymptomatic $\leq$Grade 3 laboratory abnormalities that is manageable with standard supportive care and considered not clinically significant following agreement between investigators and the sponsor or designees.

If the patient fails to meet the above-cited criteria for retreatment, initiation of the next dose of TTI-621 should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria for retreatment have been met. If toxicity does not resolve by three weeks then the patient will be considered for removal from the study. If, in the opinion of the investigator and the medical monitor, it is in the patients' best interest to continue treatment with TTI-621 then the dose of TTI-621 should be reduced by at least 1 dose level after recovery of the toxicity or toxicities in question. In such circumstances, when a dose reduction of TTI-621 is required, no re-escalation of dose will be permitted.

6.5.3 Dose Modification Guidelines for TTI-621-related toxicities

Please refer to Table 6-1 for dose delay and reduction recommendations for hematologic and non-hematologic toxicities. When the dose of TTI-621 is withheld based on the following criteria outlined below, clinical and laboratory re-evaluation should be repeated at least weekly or more frequently at investigator discretion following standard of care practice until the toxicity resolves to ≤ Grade 1 or baseline or to a level assessed to be acceptable per Section 6.5.1 and Section 6.5.2 and/or by the investigator upon agreement from the medical monitor. Upon recovery, TTI-621 may be reinitiated either at the same dose level or at a reduced dose level. In events where there are transient lab value abnormalities that, based on investigator assessment, are not clinically significant or related to disease and not the study drug, continuation of therapy without following the dose modification guideline is permissible upon discussion with the sponsor medical monitor.

Table 6-1: Dose Modifications for Dose 2 and Subsequent Doses

Clinical Scenario	Action
Grade 3 thrombocytopenia or Grade 4 thrombocytopenia lasting ≤ 72 hours*	Continue TTI-621 at the same dose when the re-treatment criterion (≥75 x10^9/L or baseline) is met; no dose intensification until no occurrence of the same event at the re-challenge of the same dose (Part 3).
Grade 4 thrombocytopenia (platelet <25 × 10^9/L) lasting >72 hours* or a platelet count ≤10 × 10^9/L at any time	Delay TTI-621 dosing until the re-treatment criterion (≥75 x10^9/L or baseline) is met; transfuse platelet prophylactically against bleeding when platelet <10K per ASCO practice guideline; Then resume TTI-621: • at the same dose if dose delay for 1 week; • at a reduced dose by 1 dose level if dose delay for > 1 week; • at a reduced dose by 1 dose level if the event recurs Dose intensification can occur only when there is no occurrence of the same event upon re-dosing of TTI-621 at the same dose for two consecutive weeks. When dose reduction occurs, no further dose intensification will be allowed (Part 3).
≥ Grade 3 thrombocytopenia (platelet <50 × 10^9/L) with clinical bleeding (more than easily controlled epistaxis, mild gum bleeding or menses)	Delay TTI-621 dosing until the re-treatment criterion (≥75 x10^9/L or baseline) is met, and then resume TTI-621 at a reduced dose by 1 dose level. No further dose intensification (Part 3) will be allowed.
Grade 4 neutropenia (ANC <500/mm ^{3}) lasting >72 hours* (unexplained by underlying disease)	Delay TTI-621 dosing when the re-treatment criterion (ANC >1000/mm^3) is met then resume TTI-621: • at the same dose if dose delay for 1 week • at a reduced dose by 1 dose level if dose delay for >1 week; • at a reduced dose by 1 dose level if the event recurs Dose intensification (Part 3) can occur only when there is no occurrence of the same event upon re-dosing of TTI-621 at the same dose for two consecutive weeks. When dose reduction occurs, no further dose intensification will be allowed.
Grade 3 febrile neutropenia lasting >72 hours*; or Grade 3 neutropenia with any clinical evidence of infection; or Grade 4 febrile neutropenia	Delay TTI-621 dosing until the re-treatment criterion (ANC >1000/mm^3) is met, then resume TTI-621 at a reduced dose by 1 dose level. When dose reduction occurs, no further dose intensification will be allowed (Part 3).

Grade 3 infusion reaction (infusion reactions lasting up to 24 hours including fevers, rigors, headaches, hypotension, dyspnea, and urticaria related to TTI-621)	The current infusion should be stopped promptly and standard care management administered. The medical monitor should be informed about the occurrence of the Gr3 event and one of the following options will be discussed following case-by-case assessment between the investigator and the medical monitor: • Restarting the infusion after medical intervention and after the patient's condition has stabilized with additional supportive care medications, • Terminating the current infusion, but re-challenging at the next weekly dose. At the re-challenge, the patient should receive premedication with corticosteroid per standard institution practice and/or established guidelines (Roselló et al., 2017); a slower rate of infusion and/or a lower dose of TTI-621 should be considered. • Permanently discontinuing the study treatment. Do not intensify dose (Part 3)
Grade 4 infusion reaction (anaphylaxis or other life-threatening reactions lasting more than 24 hours)	Permanently discontinue TTI-621
Grade 3 or greater non-hematologic toxicity related to TTI-621 with the following exceptions: • Grade 3 nausea and/or vomiting lasting <72 hours with standard supportive care • Transient Grade 3 fatigue lasting ≤72 hours • Transient asymptomatic Grade 3 laboratory abnormalities that last <72 hours with standard supportive care and considered not clinically significant following agreement between investigators and the sponsor or designees.	For Grade 3 events, delay TTI-621 dosing until the re-treatment criteria is met, then resume TTI-621 at a reduced dose by 1 dose level. No dose reduction is required for the exceptions listed. For Grade 4 events, discontinuation of TTI-621 should be considered. If, per investigator's assessment, it is in the patient's best interest to continue the treatment, TTI-621 treatment can be resumed when the AE resolves to a level that meets the re-treatment criteria Do not intensify dose (Part 3)
Grade 3 or greater non-hematologic toxicity NOT related to TTI-621	Investigator's discretion to withhold or decrease dose of TTI-621. Do not intensify dose of TTI-621 until the resolution of the AEs to Grade 1, baseline, or a level (must be ≤ Grade 2) determined to be acceptable per investigator assessment (Part 3)

Grade 3 anemia	Delay TTI-621 dosing until resolution to ≤ Grade 1 or baseline, then resume TTI-621 treatment: • at the same dose if dose delay for 1 week; • at a reduced dose by 1 dose level if dose delay for > 1 week; • at a reduced dose by 1 dose level if the event recurs • Dose intensification can occur only when there is no occurrence of the same event upon re-dosing of TTI-621 at the same dose for two consecutive weeks. When dose reduction occurs, no further dose intensification will be allowed (Part 3).
Grade 4 anemia	Discontinuation of TTI-622 should be considered. If it is in the patient's best interest to continue TTI-622 per investigator assessment, withhold dose until resolved to ≤ Grade 1 or baseline, then reduce by 1 dose level.

* When Grade 4 thrombocytopenia, Grade 4 neutropenia, or Grade 3 febrile neutropenia is first observed, hematology labs need to be repeated before the next scheduled visit to allow assessment of whether the event lasts for > 72 hours and additionally as clinically indicated per investigator discretion following standard institutional practice.

6.5.4 Intrasubject Dose Intensification (Phase 1b dose expansion Part 3)

For phase 1b Part 3, intrasubject dose intensification will be as follows:

Newly enrolled subjects: Dose intensification will start at Week 3 for subjects when the prior TTI-621 dose was associated with Grade 2 or lower treatment-related AEs. From Week 3 to Week 8, subsequent weekly doses of TTI-621 will be increased in 0.1 mg/kg/week increments as tolerated (Grade 2 or lower treatment-related AEs) and not to exceed a maximum dose of 0.5 mg/kg/week. After Week 9, additional dose intensification is not permitted.

Previously enrolled subjects: For previously enrolled subjects, dose intensification up to a maximum of 0.5 mg/kg/ week is at the investigator's discretion and should start at Week 3 if the prior TTI-621 dose was associated with Grade 2 or lower treatment-related AEs. More guidance on when to dose intensify in occurrence of AEs is provided in Table 6-1.

6.6 Intra-patient Dose Reduction and Escalation (Phase 1b Dose Optimization Part 4: DLT evaluation period)

Intra-patient dose reductions of TTI-621 are not permitted in the DLT evaluation period (Week 1-3) in the phase 1b dose optimization unless the patient experiences a DLT attributed to TTI-621. If a patient experiences a DLT during the first 21 days, treatment should be held and the event counted toward the assessment of MTD for the given cohort. These patients may continue in the study upon resolution of the toxicity at a reduced dose

level. Patients who receive a reduced dose of TTI-621 during the DLT evaluation period for reasons other than DLT will be replaced.

During phase 1b dose optimization, when the MTD or recommended phase 2 dose of TTI-621 is determined, all patients who have received TTI-621 at a dose lower than the recommended dose for a minimum of 4 weeks may dose escalate to the recommended dose in the absence of PD or unacceptable treatment-related toxicity at the investigator's discretion and with the medical monitor's approval. Patients for whom an increase in the dose of TTI-621 is being considered must have TEAEs resolve to ≤Grade 1 or baseline or to a level that is acceptable to the investigator (non-hematologic toxicity must be ≤Grade 2, hematologic toxicities must be recovered to levels above the minimum requirement for TTI-621 dosing).

6.7 Management of Clinical Events

Infusion-Related Reactions (IRR)

Premedication with an antihistamine and acetaminophen is required for all subjects prior to infusion of TTI-621. During and immediately after infusion, patients will be closely monitored for signs and symptoms of allergic reactions. In the event of a reaction of any severity during the infusion itself, the infusion should be stopped and standard institutional supportive care administered.

Grade 1 or 2: If the reaction was Grade 1 or 2 in severity and the signs and symptoms have fully resolved, the infusion may be restarted. Any patient who experiences a Grade 2 allergic reaction must receive premedication with corticosteroids per standard institutional supportive care prior to receiving subsequent infusions.

Grade 3: If a patient experiences a Grade 3 IRR, the investigator may consider the following: 1) restarting the infusion after medical intervention and after the patient's condition has stabilized with additional supportive care medications, 2) terminating the current infusion, but re-challenging at the next weekly dose, or 3) permanently discontinuing the study treatment. When re-challenge occurs, the patient should receive pre-medication with corticosteroid per standard institutional practice, and a slower infusion rate and/or a reduced dose of TTI-621 should be considered. The investigator and medical monitor will decide to continue treating patients who experienced a Grade 3 IRR on a case-by-case basis. As with all AEs of special interest, the medical monitor should be apprised of any Grade 3 or higher infusion reaction that occurs during the study.

Grade 4: If the allergic reaction was Grade 4, the patient will be permanently discontinued from treatment.

Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Administration of TTI-621 should be modified per dose modification guidance in the protocol when thrombocytopenia occurs (see Section 6.5.3). Platelet transfusion is allowed to manage severe thrombocytopenia to prevent and minimize bleeding according to the American Society of Hematology Transfusion guidelines or American Society Clinical Oncology platelet transfusion guideline. Per these guidelines, the platelet count threshold for prophylactic platelet transfusion is $<10{,}000 \times 10^9$/L. Investigators are advised to consider individual patients' bone marrow function, underlining disease, medical history, concomitant medication, and concurrent conditions and decide how to clinically manage thrombocytopenia.

6.8 Concomitant Medications and Treatment

6.8.1 Required Concomitant Treatments

All subjects must be premedicated with an antihistamine and acetaminophen prior to infusion of TTI-621. For subjects in the combination cohorts, premedication with an antihistamine and acetaminophen should be given prior to the combination agent infusion and must be repeated if the infusions of the combination agent and TTI-621 are separated by more than 4 hours.

6.8.2 Allowed Concomitant Treatments

The Investigator is permitted to use standard supportive care for symptom control or drug-related toxicity; this might include analgesics, antiemetics, electrolyte replacement, topical steroids, hydration, and/or blood product transfusions. Other prescribed medications for non-neoplastic conditions are allowed, as well as vitamins and nutritional supplements. Chronic use of steroid above a daily equivalent dose of 20 mg prednisone is not permitted on study with the exception of CTCL patients who had been on a stable dose of medium or low-potency topical steroid for 4 weeks before the first dosing of the study drug. These patients can continue to use the same dose of topical steroid for symptom control on study.

Use of selected reversible anticoagulants (low molecular weight heparin, heparin, warfarin or dabigatran) for prevention or treatment of thrombosis is permitted per the

2017 National Comprehensive Cancer Network (NCCN) guidelines, "Cancer-Associated Venous Thromboembolic Disease", with dose adjustments for thrombocytopenia per local institutional guidelines, with maintenance of platelet count >$50x10^9$/L or per local institutional standard. Use of low dose aspirin (≤81 mg day) is permitted for control of malignant thrombocytosis.

Myeloid growth factors are permitted for rescue from treatment-emergent Grade 3 or 4 neutropenia. Likewise, erythropoiesis-stimulating or megakaryopoiesis-stimulating agents may be used for treatment-emergent anemia or thrombocytopenia, respectively.

Palliative radiotherapy of limited scope (ie, not exposing a significant amount of marrow) for the purpose of symptom relief may be permitted after consultation with the Medical Monitor and will not preclude continuation of TTI-621 administration.

6.8.3 Prohibited Concomitant Treatments

No other systemic anticancer modalities (including cytotoxic, immunomodulatory, biological, ECP, topical anti-neoplastics or hormonal agents) or additional investigational agents are permitted with the following exceptions in the expansion phase only:

- In subjects with CTCL, chronic use of steroid above a daily equivalent dose of 20 mg prednisone is not permitted on study with the exception of CTCL patients who had been on a stable dose of medium or low-potency topical steroid for 4 weeks before the first dosing of the study drug. These patients can continue to use the same dose of topical steroid for symptom control on study.

Ongoing requirement for systemic corticosteroids of greater than 20 mg prednisone or equivalent is cause for exclusion at screening; the required initiation of corticosteroids during treatment (other than for treatment of an acute symptom) must be discussed with the Medical Monitor and tapered back to 20 mg prednisone or equivalent per day as soon as clinically feasible.

Use of irreversible anticoagulants is not permitted at any time during the study.

Requirement for surgery during treatment will occasion either TTI-621 treatment delay or discontinuation and will be handled case-by-case between the Investigator and Medical Monitor.

6.9 Removal of Subjects from Therapy or Assessment

Subjects will be counseled that they are free to withdraw from the study at any time. Over the course of the study, the Investigator and/or the Sponsor may withdraw a subject from treatment for any of the reasons listed below:

- disease progression (see Section 7.14.1)
- unacceptable toxicity, including any treatment-emergent Grade 4 nonhematologic toxicity considered related to TTI-621
- intercurrent illness compromising ability to fulfill protocol requirements
- requirement for alternative treatment in the opinion of the Investigator
- significant noncompliance to protocol
- withdrawal of consent by the subject
- administrative reason (eg, termination of the study by the Sponsor)
- loss to follow-up
- death

The Sponsor should be notified of the withdrawal and its reason(s). When a subject withdraws from treatment, all safety data normally required at the end of the study (ie, the end-of-treatment visit, end of study, and safety follow-up) will be obtained if possible as outlined in Sections 7.11–7.12.

7 TESTS AND EVALUATIONS

All required observations with their schedules are summarized in Appendix D. Table 1 (Part 2 and 3) and Appendix D. Table 2 (Part 4). Unless otherwise stated, the assessments below pertain to patients enrolled in both Part 3 and Part 4 of the study. Concomitant medications will be recorded from the time of informed consent through the safety follow - up visit. AEs will be recorded from the start of the first dose of study treatment through the safety follow-up visit (see Section 9.4).

Routine laboratory assessments, such as serum chemistries, hematology, coagulation and urinalysis, will be performed locally. In order to minimize required blood volume, pediatric tubes are suggested (but not required) for hematology and serum chemistries.

Special tests such as PK, ADA, and pharmacodynamic/biomarker samples will be performed centrally or as individually indicated. Additional information on the handling and processing of these samples may be found in the separate Laboratory Manual.

For subjects enrolled in the phase 1b expansion part of the study parts 2-4, there is a window of ± 2 days (2 days early or 2 days later) for any scheduled treatment days to permit holidays, travel, clinic scheduling and other delays from Week 2 and beyond. If the actual visit occurs greater than 2 days from the planned visit, that planned visit will be considered to have been missed and subjects should proceed with the next planned visit. All response assessments have an allowable window of ± 1 week. Fresh biopsies, photographs and TCR Vβ whole blood collections also have a ± 1 week allowable window to align with response assessments.

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7.1 Screening Period

Informed consent may be obtained within 30 days prior to Day 1, after which it is recommended that the subject be re-consented. The following procedures will be performed after written informed consent has been obtained and within 14 days prior to the planned start of treatment unless otherwise noted:

- physical examination including review of systems (breast/chest, extremities, head/ears/eyes/nose/throat, lymph nodes, musculoskeletal, pulmonary and skin), and height
- body weight

- ECOG performance status (see Appendix B)
- vital signs including heart rate, respiratory rate, and body temperature
- baseline disease assessment as indicated for the specific primary malignancy (see Section 7.14.1 and Appendix D. Table 3) within 28 days prior to the planned start of treatment. CTCL: mSWAT, CAILS (local disease only) and central photographs.
    - Leukemia and lymphoma with marrow involvement: bone marrow aspirate for routine morphology, flow cytometry, CD47 expression and receptor occupancy (not required for Part 4)
    - CTCL: photographs of tumor lesions will be captured at the clinical site(s) using standardized photographic equipment, methodologies and services provided by Canfield Scientific, Inc. (Parsippany, New Jersey). Further detail for study photography will be provided in the supplied Canfield User Manual
- CTCL and PTCL (Part 3 only): Radiographic disease assessments for CTCL and PTCL will be submitted for central review (central results are not required for enrollment). Please refer to the Imaging Manual. Part 4 will not require submission of scans for central review in real time but retrospective submissions might be requested by sponsor.
- CTCL and PTCL (Part 3 only): Tumor tissue will be submitted for central review for subjects with CTCL (not including SS) and PTCL to confirm the diagnosis (central disease confirmation not required for enrollment). For subjects with SS, peripheral blood is acceptable. Archival tissue may be provided. Refer to the Laboratory Manual for additional details.
- resting 12-lead ECG
- hepatitis B (HBsAg and HBcAb) and C (HCV Ab) panel
- serum pregnancy test for women of childbearing potential
- serum chemistries, including alkaline phosphatase, albumin, ALT, AST, bilirubin (direct, indirect, and total), blood urea nitrogen (BUN), creatinine, glucose, lactate dehydrogenase (LDH), total protein, uric acid, and electrolytes (sodium, potassium, calcium, chloride, bicarbonate, phosphorus)
- hematology, including WBC with 5-part automated differential, hemoglobin, RBC, absolute reticulocytes, platelets
- coagulation panel (prothrombin time, partial thromboplastin time, INR, and plasma fibrinogen)
- thyroid-stimulating hormone (TSH; only for subjects in the nivolumab combination cohort)
- Tumor tissue for biomarker analysis: fresh tumor biopsy tissue, if feasible, to be performed for all patients. If tumor biopsy is not feasible archival tissue is

acceptable. For subjects with SS, peripheral blood is acceptable, if a fresh biopsy is not possible. Refer to the Laboratory Manual for additional details.

The following complete historical subject information will be captured prior to Day 1:

- medical history
- history of malignancy, including histologic or cytologic confirmation of the primary malignancy, primary diagnosis date, prior treatments for the malignancy, and documentation of prior response and relapse status
- ongoing medications including those administered within 14 days prior to the planned start of treatment
- QOL via FACT-G questionnaire (all tumor types) and SKINDEX29 questionnaire (subjects with CTCL)

7.2 Day 1 Pre-infusion

For the TTI-621 monotherapy cohorts, the procedures listed below will be performed at the indicated time relative to the infusion of TTI-621. For subjects in the combination cohorts, the procedures below will be performed relative to the infusion of the combination partner. Except where noted, these assessments can be performed up to 24 hours pre-infusion. Baseline testing are assessments preformed within 3 days prior to or on Day 1 pre-dose. Subjects with screening laboratories within 3 days prior to dosing for a particular variable need not repeat the test on Day 1. To proceed with Day 1 infusion, subjects should meet eligibility criteria.

- symptom driven physical examination (as before) and ECOG score
- body weight
- vital signs prior to infusion (performed per the institutional standard of care)
- resting 12-lead ECG within 60 minutes prior to infusion (± 30 minutes)
- serum chemistries (as before)
- hematology (as before)
- serum for PK 30 minutes pre-infusion (see Section 7.14.2)
- biomarkers (± 15 minutes; see Laboratory Manual for details of sample splitting, preparation, and shipping)
    - serum for cytokine/chemokine panel (not required for Part 4).
    - serum for anti-tumor antibodies (not required for Part 4).
    - whole blood TCR Vβ sequencing (not required for Part 4).
    - whole blood for receptor occupancy

  - whole blood for innate and adaptive response assay (not required for Part 4).

- serum for ADA prior to infusion (± 15 minutes)
- urinalysis (color, appearance, specific gravity, pH, glucose, bilirubin, ketones, occult blood, protein)
- coagulation for Part 4 only

Subjects in the combination cohorts will also undergo the following additional assessments. These assessments are to be done after the combination partner infusion and prior to the TTI-621 infusion:

- vital signs 60 minutes (± 15 minutes) after completion of the combination partner infusion (only if the combination partner and TTI-621 are administered more than 60 minutes apart); performed per the institutional standard of care
- vital signs prior to TTI-621 infusion ; performed per the institutional standard of care

7.3 Day 1 Post-TTI-621 infusion (see Table 7-1)

- vital signs at completion of infusion (approximately 60 minutes after Time 0 [± 15 minutes]) and 2 and 4 hours after Time 0 [± 15 minutes])
- 12-lead ECG within approximately 30 minutes of the completion of infusion (i.e., 60–90 minutes after Time 0)
- Serum for PK:
  - For Part 3: at completion of infusion (approximately 60 minutes after Time 0), 2 hours and 4 hours after Time 0, Day 2 (approximately 24 hours after Time 0). See Table 7-2 and Appendix D. Table 2.
  - For Part 4: at completion of infusion (approximately 60 minutes after Time 0), 2 hours, 4 hours after Time 0, Day 2 (approximately 24 hours after Time 0) and Day 4 (approximately 72 hours after Time 0). See Table 7-2 and Appendix D. Table 2. If a priming regimen is used, see Appendix F for revised sampling timepoints.
- Hematology:
  - For Part 3: - at completion of infusion (approximately 60 minutes after Time 0), 2 hours, and 4 hours after Time 0 (± 15 minutes).
  - For Part 4: at completion of infusion (approximately 60 minutes after Time 0), 2 hours, 4 hours after Time 0 (± 15 minutes), Day 2 (approximately 24 hours after Time 0) and Day 4 (approximately 72

hours after Time 0), see Appendix D. Table 2. If a priming dose is used, see Appendix F for revised sampling timepoints.

- biomarkers (± 15 minutes; see Laboratory Manual for details of sample splitting, preparation, and shipping):
  - serum for cytokine/chemokine panel at completion of infusion (approximately 60 minutes after Time 0) and 4 hours after Time 0, (not required for Part 4).
  - whole blood for receptor occupancy at completion of infusion (approximately 60 minutes after Time 0)
- AEs
- concomitant medications

Table 7-1: Week 1 Temporal Summary of Infusion and Post-infusion Assessments

T = 0	**T 0–60 min**	**T + 60 min**	**T + 2 hr**	**T + 4 hr**	**T + 24 hr**	**T + 72 hr**
Start TTI-621 infusion	→	End infusion				
	- - - - - - - - - - - Monitor for infusion reactions - - - - - - - - - - -					
		Vital signs	Vital signs	Vital signs		
		ECG				
		Receptor occupancy				
		Pharmacokin.	Pharmacokin.	Pharmacokin.	Pharmacokin.	Pharmacokin. (Part 4 only)
		Hematology	Hematology	Hematology	Hematology (Part 4 only)	Hematology (Part 4 only)
		Cytokines/ chemokines (Part 3 only)		Cytokines/ chemokines (Part 3 only)		

7.4 Week 2

On Day 1 of Week 2 (Day 8 of treatment), the below tests and observations will be performed. For the TTI-621 monotherapy cohorts, assessments will be performed at the indicated time relative to the infusion of TTI-621. For subjects in the combination cohorts, assessments will be performed relative to the infusion of the combination partner, as applicable. All of these assessments can be performed up to 24 hours pre-infusion, with the exception of vital signs, PK, and biomarkers. Post-infusion procedures will be relative to the TTI-621 infusion.

- symptom-driven physical examination and ECOG score
- body weight
- vital signs prior to infusion and at completion of infusion (60 minutes after Time 0 [(± 15 minutes]). For subjects in the combination cohorts, the latter timepoint (60 minutes after Time 0) is to be done only if the combination partner and TTI-621 are administered more than 60 minutes apart; performed per the institutional standard of care. For subjects under Part 4, vitals are not required at end of infusion. Refer to Appendix D. Table 2.
- biomarkers (± 15 minutes; see Study Manual for details of sample splitting, preparation, and shipping):
    - serum for cytokine/chemokine panel (pre-dose), not required for Part 4
    - whole blood for receptor occupancy (pre-dose) for Part 3 and 4. For Part 4, if a priming dose is used see Appendix F for revised sampling timepoints.
- Serum for PK:
    - For Part 3 and Part 4: serum for PK trough levels (pre-dose). See Appendix D. Table 1 and Appendix D. Table 2. If a priming regimen is used, see Appendix F for revised sampling timepoints.
- Hematology:
    - For Part 3: pre-dose (results must be available prior to start of infusion). Further hematologic monitoring should be instituted at the discretion of the treating Investigator.
    - For Part 4: pre-dose (results must be available prior to start of infusion) and 4 hours after Time 0 (± 15 minutes). Day 2 (approximately 24 hours after Time 0) assessments are required if clinically indicated, in the event that ≥ Grade 4 thrombocytopenia is observed on day 1 or there are any other clinical conditions indicated for a follow-up lab at the investigator discretion. Further hematologic monitoring should be instituted at the discretion of the treating

Investigator. If a priming dose is used, see Appendix F for revised sampling timepoints.

- serum chemistries
- AEs
- concomitant medications
- coagulation panel only for Part 4

7.5 Week 3

On Day 1 of Week 3 (Day 15 of treatment), the below tests and observations will be performed. For the TTI-621 monotherapy cohorts, assessments will be performed at the indicated time relative to the infusion of TTI-621. For subjects in the combination cohorts, assessments will be performed relative to the infusion of the combination partner, as applicable. All of these assessments can be performed up to 24 hours pre-infusion, with the exception of PK and vital signs. For Part 3 only, if intrasubject dose intensification occurs at this visit please also refer to Section 7.6 for additional assessments.

- symptom driven physical examination and ECOG score
- body weight
- vital signs prior to infusion and at completion of infusion (60 minutes after Time 0) [(± 15 minutes]). For subjects in the combination cohorts, the latter timepoint (60 minutes after Time 0) is to be done only if the combination partner and TTI-621 are administered more than 60 minutes apart; performed per the institutional standard of care. For subjects under Part 4, vitals are not required at end of infusion. Refer to Appendix D. Table 2.
- Serum for PK:
  - For Part 3: serum for PK trough levels (pre-dose)
  - For Part 4: serum for PK trough levels (pre-dose). If a priming dose is used see Appendix F for revised sampling timepoints.
- Hematology:
  - For Part 3: pre-dose (results must be available prior to start of infusion). Further hematologic monitoring should be instituted at the discretion of the treating Investigator.
  - For Part 4: pre-dose (results must be available prior to start of infusion) and 4 hours after Time 0 (± 15 minutes). Day 2 (approximately 24 hours after Time 0) assessments are required if clinically indicated, in the event that ≥ Grade 4 thrombocytopenia is observed on day 1 or there are any other clinical conditions indicated for a follow-up lab at the investigator discretion. Further hematologic

monitoring should be instituted at the discretion of the treating Investigator. If a priming dose is used, see Appendix F for revised sampling timepoints.

- serum chemistries
- AEs
- concomitant medications
- coagulation panel only for Part 4
- biomarkers (± 15 minutes; see Study Manual for details of sample splitting, preparation, and shipping):
    - For Part 4: If a priming dose is used additional whole blood for receptor occupancy is required. See Appendix F for additional sampling timepoints.

7.6 TTI-621 Intrasubject Dose Intensification – Additional Assessments Every Week of Dose Intensification (only applicable to Part 3)

For subjects who are dose intensified at Week 3 through Week 8, the following assessments are required on Day 1, only if not already part of the scheduled weekly visit. For the TTI-621 monotherapy cohorts, assessments will be performed at the indicated time relative to infusion of TTI-621. For subjects in the combination cohorts, pre-infusion assessments will be performed relative to the start of the combination partner infusion, as applicable.

- serum for PK at end of infusion and 4 hours after Time 0 (see Table 7-2)
- whole blood for receptor occupancy: pre-infusion and at end of infusion (approximately 60 minutes after Time 0, ± 15 minutes)
- hematology at 4 hours after Time 0. Additional hematologic monitoring should be instituted at the discretion of the treating Investigator.
- serum chemistries at 4 hours after Time 0

7.7 Week 4

On Day 1 of Week 4 (Day 22 of treatment), the below tests and observations will be performed. For the TTI-621 monotherapy cohorts, assessments will be performed at the indicated time relative to the infusion of TTI-621. For subjects in the combination cohorts, assessments will be performed relative to the infusion of the combination partner, as applicable. All of these assessments can be performed up to 24 hours pre-infusion, with the exception of vital signs and PK. For Part 3 only, if intrasubject dose intensification occurs at this visit please also refer to Section 7.6 for additional assessments.

- symptom driven physical examination and ECOG score
- body weight
- vital signs prior to infusion and at completion of infusion (60 minutes after Time 0 [(± 15 minutes]). For subjects in the combination cohorts, the latter timepoint (60 minutes after Time 0) is to be done only if the combination partner and TTI-621 are administered more than 60 minutes apart; performed per the institutional standard of care. For subjects under Part 4 vitals are not required at end of infusion. Refer to Appendix D. Table 2.
- urine or serum pregnancy test for women of childbearing potential
- Serum for PK:
    - For Part 3: serum for PK trough levels (pre-dose)
    - For Part 4: serum for PK trough levels (pre-dose). If a priming regimen is used see Appendix F for revised sampling timepoints.
- Hematology:
    - For Part 3: pre-dose (results must be available prior to start of infusion). Further hematologic monitoring should be instituted at the discretion of the treating Investigator.
    - For Part 4: pre-dose (results must be available prior to start of infusion). Further hematologic monitoring should be instituted at the discretion of the treating Investigator. If a priming regimen is used, see Appendix F for revised sampling timepoints.
- serum chemistries
- serum for ADA
- AEs
- concomitant medications
- coagulation panel only for Part 4
- resting 12-lead ECG within 60 minutes prior to infusion (± 30 minutes) only for Part 4
- biomarkers (± 15 minutes; see Study Manual for details of sample splitting, preparation, and shipping):
    - For Part 4: If a priming dose is used additional whole blood for receptor occupancy is required. See Appendix F for additional sampling timepoints.

7.8 Week 5-7

On Day 1 of Week 5, the below tests and observations will be performed. For the TTI-621 monotherapy cohorts, assessments will be performed at the indicated time relative to the infusion of TTI-621. For subjects in the combination cohorts, assessments will be performed relative to infusion of the combination partner, as applicable. All assessments can be performed up to 24 hours pre-infusion, with the exception of PK. For Part 3 only, if intrasubject dose intensification occurs at this visit please also refer to Section 7.6 for additional assessments.

- symptom driven physical examination and ECOG score
- vital signs, performed per the institutional standard of care
- body weight
- Part 3 and Part 4: hematology (results must be available prior to study drug). For Part 4, if a priming dose is required see Appendix F.
- Part 3 and Part 4: serum for PK trough levels (pre-dose). For Part 4, if a priming dose is required see Appendix F.
- AEs
- concomitant medications

7.8.1 Week 5 (Part 4 only)

The following assessments are also required in addition to the week 5 assessments specified above, for Part 4 only.

- biomarkers (± 15 minutes; see Study Manual for details of sample splitting, preparation, and shipping):
    - For Part 4: If a priming dose is used additional whole blood for receptor occupancy is required. See Appendix F for additional sampling timepoints.

7.8.2 Week 6 (Part 4 only)

The following assessments are also required in addition to the week 6 assessments specified above, for Part 4 only.

- Serum for PK – at completion of infusion (approximately 60 minutes after Time 0), 2 hours and 4 hours after Time 0 (± 15 minutes), Day 2 (approximately 24 hours after Time 0) and Day 4 (approximately 72 hours after Time 0). See Table 7-2.

- Whole blood for receptor occupancy – pre-dose and at end of infusion (approximately 60 minutes after Time 0)

7.8.3 Week 7 (Part 4 only)

The following assessments are also required in addition to the week 7 assessments specified above, for Part 4 only.

- Whole blood for receptor occupancy pre-dose

7.9 Week 8

The below tests and observations will be performed on Day 1 of Week 8 unless otherwise stated. For subjects in the monotherapy cohorts, the procedures listed below will be performed at the indicated time relative to TTI-621 infusion. For subjects in the combination cohorts, pre-infusion procedures will be relative to the combination agent infusion, where applicable. Post-infusion procedures will be relative to the TTI-621 infusion. All assessments can be performed up to 24 hours pre-infusion, with the exception of PK and biomarkers.

- symptom driven physical examination and ECOG score
- vital signs, performed per the institutional standard of care
- body weight
- disease assessment at the end of the week (see Appendix D. Table 3)
    - For CTCL and PTCL subjects, central submission of radiographic disease assessments is required. Part 4 will not require submission of scans for central review in real time but retrospective submissions might be requested by sponsor.
    - CTCL subjects only: mSWAT, CAILS (if applicable) and photographs
- Fresh tumor sample from an identified target lesion (CTCL subjects: required if feasible to perform biopsy, all other tumor types: optional).
- Peripheral blood and blood smear for central pathology review (See Appendix D. Table 3). Refer to the Laboratory Manual for additional details; not required for Part 4
- resting 12-lead ECG
- Post-dose: QOL by FACT-G (all subjects) and SKINDX29 (CTCL only)
- urine or serum pregnancy test for women of childbearing potential
- serum chemistries

- hematology (results must be available prior to start of infusion). Further hematologic monitoring should be instituted at the discretion of the treating investigator.
- serum for PK (see Table 7-2):
    - Part 3: trough levels pre-infusion and completion of infusion (approximately 60 minutes after the start of infusion [i.e., Time 0]), 2 hours and 4 hours after Time 0, Day 2 (approximately 24 hours after Time 0), and Day 4 (approximately 72 hours after Time 0)
    - Part 4: trough levels pre-infusion
- biomarkers (± 15 minutes; see Study Manual for details of sample preparation and shipping):
    - bone marrow aspirate for receptor occupancy (only for subjects with bone marrow based disease), to align with the response assessments. Not required for Part 4
    - serum for cytokine/chemokine panel pre-infusion, at completion of infusion (approximately 60 minutes after Time 0), 4 hours after Time 0, and Day 2 (approximately 24 hours after Time 0); not required for Part 4.
    - Part 3: whole blood for receptor occupancy pre-infusion and at completion of infusion (approximately 60 minutes after Time 0); not required for Part 4.
    - whole blood for innate and adaptive response assay pre-infusion, not required for Part 4
    - whole blood for TCR Vβ sequencing pre-infusion, not required for Part 4
- urinalysis (Part 3 only)
- coagulation (Part 4 only)
- serum for ADA analysis
- AEs
- concomitant medications

7.10 Weeks 9 and Higher

7.10.1 Phase 1b Part 3

The following assessments are applicable for Part 3.

For subjects in the monotherapy cohorts, the procedures listed below will be performed at the indicated time relative to the infusion of TTI-621. For subjects in the combination cohorts, pre-infusion procedures will be relative to the combination agent infusion, where applicable. Post-infusion procedures will be relative to the TTI-621 infusion. All assessments can be performed up to 24 hours pre-infusion, with the exception of PK and biomarkers. The below testing intervals represent a minimum; subjects with an ongoing abnormality should be monitored more frequently as clinically indicated.

- symptom driven physical examination and ECOG score Day 1 of Week 12 and every 4 weeks thereafter
- vital signs, performed per the institutional standard of care
- body weight measured every other week (Week 10, 12, etc.). After Week 8, the weight taken at the prior visit may be used to calculate dose (e.g. weight at Week 8 used for Week 9 dosing)
- disease assessment (see Appendix D. Table 3) at the end of Weeks 16 and 24, followed by every 12 weeks (Weeks 36, etc.) or at the point that clinical progression is observed or suspected.
    - For CTCL and PTCL subjects, central submission of radiographic disease assessments is required.
    - CTCL subjects only: mSWAT, CAILS (if applicable) and photographs at time of disease assessments
    - Peripheral blood and blood smear for central pathology review for SS subjects only. Refer to the Laboratory Manual and to Appendix D. Table 3 for additional details.
- Week 16 pre-infusion: fresh tumor sample from an identified target lesion for CTCL subjects only
- resting 12-lead ECG Day 1 of Weeks 16 and 24
- QOL by FACT-G (all subjects) and SKINDX29 (CTCL only): post-dose on Week 16 and 24, and then every 12 weeks thereafter
- urine or serum pregnancy test for women of childbearing potential Day 1 of Week 12 and every 4 weeks thereafter
- serum chemistries Day 1 of Week 12 and every 4 weeks thereafter
- hematology Day 1 of every week (results must be available prior to start of infusion). Further hematologic monitoring should be instituted at the discretion of the treating investigator.

- serum for PK (see Table 7-2):
    - Day 1 of Week 9 and every week through Week 16 inclusive: trough level (pre-infusion)
- biomarkers (± 15 minutes; see Study Manual for details of sample preparation and shipping):
    - Day 1 of Week 9 (pre-infusion): serum for cytokine/chemokine panel
    - Day 1 of Week 16 (pre-infusion): whole blood TCR Vβ sequencing
    - Day 1 of Week 16 only (pre-infusion): anti-tumor antibodies
    - Day 1 of Week 9 (pre-infusion): whole blood for receptor occupancy
- TSH on Day 1 of Week 12 and every 12 weeks thereafter (only for subjects in the nivolumab combination cohort)
- serum for ADA analysis pre-infusion on Day 1 of Week 12 and every 4 weeks
- AEs
- concomitant medications

7.10.2 Phase 1b Part 4

The following assessments are applicable for patients under Part 4. Refer to Appendix D. Table 2. The procedures listed below will be performed at the indicated time relative to the infusion of TTI-621. All assessments can be performed up to 24 hours pre-infusion, with the exception of PK and biomarkers.

- Day 1 of Week 12, and every 4 weeks thereafter:
    - coagulation, symptom driven from week 16 onward
    - resting 12-lead ECG
    - urine or serum pregnancy test for women of childbearing potential
    - serum chemistries
- body weight measured every other week (Week 10, 12, etc.). After Week 8, the weight taken at the prior visit may be used to calculate dose (e.g. weight at Week 8 used for Week 9 dosing)
- vital signs pre-infusion, performed per the institutional standard of care weekly
- disease assessment (see Appendix D. Table 3) at the end of Weeks 16 and 24, followed by every 12 weeks (Weeks 36, etc.) or at the point that clinical progression is observed or suspected.

  - central submission of radiographic disease assessments is not required for central review in real time but retrospective submissions might be requested by sponsor.
  - mSWAT, CAILS (if applicable) and photographs
  - QOL by FACT-G and SKINDX29
- hematology Day 1 of every week (results must be available prior to start of infusion). Further hematologic monitoring should be instituted at the discretion of the treating investigator.
- symptom driven physical examination/ECOG score Day 1 of every week
- AEs
- concomitant medications
- serum for PK (see Table 7-2):
  - Day 1 of Week 9 and every week through Week 16 inclusive: trough level (pre-infusion)
- biomarkers (± 15 minutes; see Study Manual for details of sample preparation and shipping):
  - Week 16 pre-infusion: fresh tumor sample if feasible from the same lesion as screening or from a nearby lesion for CTCL subjects only
  - whole blood for receptor occupancy pre-infusion on Day 1 of Week 12 and 16.
- serum for ADA analysis pre-infusion on Day 1 of Week 12 and every 4 weeks

7.11 End-of-Treatment Visit

Within 1 week following the final dose of TTI-621 (or at the time of premature discontinuation of treatment), the following procedures will be performed:

- physical examination and ECOG score
- body weight
- vital signs
- disease assessment (if not performed within the last 8 weeks)
- QOL by FACT-G (all subjects) and SKINDX29 (CTCL only)
- resting 12-lead ECG
- serum for PK
- serum chemistries
- hematology

- coagulation panel
- TSH (only for subjects in the nivolumab combination cohort)
- urinalysis
- serum for ADA analysis
- biomarkers (see Study Manual for details of sample preparation and shipping):
    - serum for cytokine/chemokine panel (not required for Part 4)
    - whole blood for innate and adaptive response assay (not required for Part 4)
- AEs
- concomitant medications
- peripheral blood and blood smear for central pathology for SS patients (Part 3 only). Refer to the Laboratory Manual and to Appendix D. Table 3 for additional information.

7.12 Safety Follow-up Visit

Approximately 30 days after the final dose of TTI-621 (± 2 days), the following will be performed. If treatment-emergent abnormalities are present at the end-of-treatment visit, repeat pertinent labs or studies:

- symptom driven physical examination and ECOG score
- body weight
- vital signs
- serum chemistries
- hematology
- TSH (only for subjects in the nivolumab combination cohort)
- serum for ADA analysis; subjects who are seropositive at safety follow-up, should be monitored at least quarterly for 1 year post study to assess persistence of antibodies
- status of unresolved AEs

7.13 Long-term Follow-up (Expansion Phase Only)

For a period of 1 year following the safety follow-up visit, subjects treated in the expansion phase will be contacted at least quarterly (±1 week) via routine clinic visit and/or telephone call to assess the following:

- subsequent anticancer therapies
- status of any ongoing/chronic AEs that were treatment-emergent
- persistence of ADA in those subjects who seroconverted
- date of disease progression (if not documented on study)
- survival status

7.14 Procedures for Special Tests

7.14.1 Disease Assessment

Disease assessments for individual malignancy types are detailed in Appendix D. Table 3.

Response Criteria
Tumor response assessment for lymphomas (including PTCL) in both the escalation and expansion phases will utilize the Lugano Classification (Cheson et al., 2014), including the 2016 refinement of these criteria (Cheson et al., 2016). A response will be defined as an objective status of partial remission (PR) or complete remission (CR) for subjects evaluated by computed tomography (CT)-based criteria and complete metabolic response (CMR) or partial metabolic response (PMR) for subjects evaluated by positron emission tomography -CT based criteria. For CTCL, a response will be defined as PR or CR in any of the organ systems individually (skin, viscera, blood or lymph nodes). Additionally, a global response incorporating each organ system will be compiled per the Olsen criteria (Olsen et al., 2011). Radiographic disease assessments for CTCL and PTCL will be submitted for central review for those subjects enrolled to phase 1b Part 3. The subjects enrolled to phase 1b Part 4 will not require submission of scans for central review in real time but might be requested by sponsor retrospectively.
For the additional malignancies in the expansion phase, the following classification systems will be employed:

- AML and ALL – Revised Recommendations of the International Working Group for trials in AML (Cheson et al., 2003)

- CLL – International Workshop on CLL update of the NCI 1996 Guidelines (Hallek et al., 2008)
- MDS/MPN – An International Consortium Proposal of Uniform Response Criteria for Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) in Adults (Savona et al., 2015)
- Multiple Myeloma – International Uniform Response Criteria for Multiple Myeloma (Durie et al., 2006)
- CTCL – Clinical Endpoints and Response Criteria in Mycosis Fungoides and Sezary Syndrome (Olsen et al., 2011)
- SCLC – Adaptation of the Immune-Related Response Criteria: irRECIST (Bohnsack et al., 2014)

Pseudoprogression or Indeterminate Response

Some therapeutic agents, particularly immunotherapeutics, display different patterns of anti-tumor response, which may include a period of increasing tumor burden followed by a response, stable disease followed by slow decline in tumor burden, or even a response in the presence of new lesions (Cheson et al., 2016; Chow, 2013; Wolchok et al., 2009). Immune-mediated responses may take longer to manifest than those from cytotoxic agents. In other cancer settings, a phenomenon called "tumor flare" or pseudoprogression has also been described, in which increased contrast enhancement and hyperintensity is observed on posttreatment MRI scans (fluid - attenuated inversion recovery, or FLAIR) which represents a biologic effect on the tumor and its microenvironment and which stabilizes or diminishes over time (Batchelor, 2012).

In order to avoid falsely assigning disease progression during the expansion phase of the study, a subject whose radiologic disease assessment is indicative of progression may, at the discretion of the Investigator and Medical Monitor, be considered "Indeterminate" in the case report forms and continue on treatment pending a repeat scan 4 to 6 weeks later, if all of the following criteria are met:

- absence of symptomatic or clinical progression
- stable performance status
- adequate tolerance to TTI-621 therapy
- treating beyond progression does not delay an intervention felt to be in the subject's best interest

If the second confirmatory scan indicates unequivocal disease progression, the subject will be discontinued from treatment. The date of the first scan indicating progression will be used for analysis purposes. If however the second scan indicates a reduction in tumor burden or stable disease from the baseline scan, the subject may continue on treatment in the absence of unacceptable toxicity or other reason for treatment discontinuation.

Notwithstanding, the Investigator is free to remove the subject from treatment at any time during the study if it is felt to be in the subject's best interest.

7.14.2 PK

In both the escalation and expansion phases (Part 2), serial blood sampling will take place in conjunction with the first and sixth weekly infusion of TTI-621 (i.e., Days 1 and 36 of study) to estimate the PK profile of TTI-621. Subsequent sampling after the first week will be limited to "trough" levels (30 minutes pre-dose). A sample will also be taken at EOT.

For phase 1b Part 3 only, serial blood sampling will take place in conjunction with the first and eighth weekly infusion of TTI-621, a time at which mandatory intra-subject dose intensification for newly enrolled subjects is anticipated to be completed. This sampling will be performed to evaluate the PK profile of TTI-621 following dose-intensification, and after repeat dosing. Subsequent sampling will be limited to "trough" levels at Week 9 through Week 16 inclusive. A sample will also be taken at EOT.

For phase 1b Part 4, for subjects enrolled in cohorts without priming doses, serial blood sampling will take place in conjunction with the first and sixth weekly infusion of TTI-621(i.e., Days 1 and 36 of study) to estimate the PK profile of TTI-621 with further dosing optimization. For subjects enrolled in cohorts with priming dose regimen under phase 1b Part 4 receiving a single priming dose on Week 1, serial blood sampling will take place on Week 2, following administration of the highest stable dose and on the sixth weekly infusion of TTI-621 to estimate the PK profile of TTI-621 with further dosing optimization. Subsequent sampling for all phase 1b Part 4 cohorts, will be limited to "trough" levels at Week 9 through Week 16 inclusive. A sample will also be taken at EOT.

If there is a delay in infusion administration (i.e., duration of TTI-621 infusion is greater than 60 minutes), the end-of-infusion PK sample should be drawn at the time the infusion is complete (prior to flush). However, all subsequent timepoints should

not be adjusted and should be collected relative to the start of TTI-621 infusion as summarized in Table 7-2.

Whole blood will be collected at each time point and prepared as outlined in the separate Laboratory Manual.

Table 7-2: Summary of PK Sampling Times

Week	Day	Nominal Time	Allowable Time Window
N	1	Pre-infusion (within 30 min)	± 15 min
	1	EOI (60 min)§	+5 min
	1	T + 2 hr§	± 15 min
	1	T + 4 hr§	± 15 min
N	2	T + 24 hr§	± 6 hrs
N	4	T + 72 hr§	± 24 hrs
N	1	trough (30 min pre-infusion)	± 15 min
EOT		Within 1 week following final dose	

EOI = immediately after the end of infusion (i.e., prior to flush)
EOT = end of treatment
N = any week where the listed timepoints are applicable
§ Relative to the start of first TTI-621 infusion

CCI

- CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8 PLANNED ANALYSES

A separate Statistical Analysis Plan will provide final specific details on the analytical methods and data displays.

8.1 Study Endpoints

8.1.1 Escalation Phase

Primary

- Incidence and severity of AEs

Secondary

- PK profile, PD, ADA

8.1.2 Expansion Phase, Part 2 and Part 3

Primary

- Incidence and severity of AEs

Secondary

- PK profile, PD, ADA
- Overall response rate, duration of response, and progression-free survival
- Part 3: CTCL and PTCL: organ system overall response rate – 2 analyses within each cohort

8.1.3 Expansion Phase, Part 4

Primary

- Incidence and severity of AEs

Secondary

- PK profile, PD, ADA
- Overall response rate and duration of response
- CTCL: organ system overall response rate

8.2 Analysis Populations

Safety Analysis Set

The Safety Analysis Set will be used for the analysis of safety data in this study and will consist of all subjects who receive at least 1 dose of TTI-621.

Full Analysis Set

The Full Analysis Set will serve as the primary population for all efficacy-related data, with the exception of the analysis of overall response, for which the Response-Evaluable Set will be primary, and the Full Analysis Set will be secondary. The Full Analysis Set is a subset of all enrolled subjects, with subjects excluded for the following reasons:

- failure to receive at least 1 dose of TTI-621
- lack of baseline data for those analyses that require baseline data

Response-Evaluable Set

The Response-Evaluable Set will serve as the primary population for the analysis of overall response. The Response-Evaluable Set is a subset of the Full Analysis Set, with subjects excluded if they have no post-baseline assessment of overall response.

Per-protocol Set

A supportive analysis may be performed by excluding subjects with important deviations from the protocol that may substantially affect the results of the primary efficacy analyses. The final determination on protocol violations, and thereby the composition of the Per-protocol Set, will be made prior to locking the clinical database and final analysis and will be documented in the statistical analysis plan (SAP).

PK-evaluable Set

The PK-evaluable Set consists of treated subjects with adequate blood sampling to estimate at least 1 PK parameter.

8.3 Determination of Sample Size

Escalation Phase

Up to 6 subjects may be enrolled in each dose cohort evaluated during the escalation phase. The minimum number of subjects enrolled in each cohort and the dose-step increments between adjacent cohorts will be based on a standard 3 + 3 dose escalation scheme (Section 3.2). A maximum of 36 subjects will be enrolled between up to 6 dose cohorts. The actual number enrolled is dependent upon the observed safety profile, which will determine the number of subjects per dose cohort, as well as the number of dose escalations required to achieve the MTD.

Expansion Phase

For the purpose of broadly characterizing preliminary anti-tumor activity, a 95% one-sided confidence interval will be calculated according to Table 8-1 for each cohort of 12 to 15 subjects evaluated. The original number of subjects was chosen largely based on clinical and feasibility considerations in light of the number of distinct cohorts to be evaluated. Although the number of subjects to be enrolled in an individual cohort is limited, the number of responses and any other indicators of clinical benefit that are observed within a cohort can be used to assess in a preliminary manner whether the true overall response rate is either unacceptably low or sufficiently high to warrant further evaluation in this or a future study. For example, if 12 subjects are enrolled within a cohort, the probability of observing no responses is low (i.e., < 1%) when the true overall response rate is 40% or higher. Similarly, the probability of observing 3 or more responses is high (i.e., 92%) when the true overall response rate is 40% or higher. When the true overall response rate is only 10%, the probability of observing 3 or more responses is 11%.

After a preliminary evaluation of both the tolerability of treatment and any early signs of clinical benefit as characterized by overall response rate, prolonged progression-free intervals, or clearance of minimal residual disease, a hematologic disease cohort may be expanded (and, if appropriate, further refined by disease characteristics) to a maximum of 40 subjects to further evaluate clinical benefit.

Table 8-1: 95% Lower Confidence Limits for Response Rate

	Number of Responses					
Number of Subjects	**3**	**4**	**5**	**6**	**7**	**8**
10	9%	15%	22%	30%	39%	49%
11	8%	14%	20%	27%	35%	44%
12	7%	12%	18%	25%	32%	39%
13	7%	11%	17%	22%	29%	35%
14	6%	10%	15%	21%	26%	33%
15	6%	10%	14%	19%	24%	30%

For the phase 1b portion (Part 2) of the study, the cohort size for selected cohorts has been increased to 40 subjects. This is to improve the precision of the overall response rate (ORR) estimate. For example, for an ORR of 30%, in 10 subjects, the lower confidence limit (LCL) of a 95% one-sided confidence interval is 8.7%, or a distance of 21.3% (30-8.7) from the ORR. When the sample size is increased to 40 for the same ORR, the LCL is 18.3%, or a distance of 11.7% (30-18.3) from the ORR. This anticipated improvement in the precision of the point estimate will be particularly important given the relative heterogeneity of the enrolled population.

Expansion Phase Part 3: CTCL and PTCL Cohorts

For the phase 1b (Part 3) expansion cohorts for CTCL and PTCL, the cohort size has been selected based upon a Simon optimal 2-stage design, with the low and high boundaries of the response rate being 10% (not effective) and 30% (warrants further study) respectively, and a power of 90% and an alpha of 0.05. The calculations were performed using PASS 14 (NCSS, 2015) and the Optimum design chosen. The total sample size is 35 subjects per cohort under the scenario described below. For the first stage, a total of 18 subjects will be enrolled in each cohort. At the end of Stage 1, if 2 or fewer responders are observed per cohort, enrollment in this cohort will be terminated, otherwise, enrollment will proceed to the second stage and an additional 17 subjects will be enrolled per cohort for a total of 35 subjects per cohort. At the end of the second stage, if 6 or fewer responders are observed per cohort, the drug will be rejected for further testing in this indication. The probability of early termination (PET) = 0.734 at the end of the first stage if the true response rate is less than 10%.

N1	R1	PET	N	R	Average N	Alpha	Beta
18	2	0.734	35	6	22.53	0.047	0.098

Part 4 - Phase 1b Dose Optimization

Up to 6 DLT evaluable subjects may be enrolled at each dose level evaluated during the escalation phase. The number of subjects enrolled at each dose level and the dose-step increments between adjacent dose levels will be based on a 3 + 3 dose escalation scheme (Section 3.2.2). Once the MTD or a recommended dose is estimated (with the required six DLT-evaluable patients at that dose level), an additional six patients will be treated at that dose level (for a total of twelve patients). These additional patients will allow further examination of the safety and tolerability of the dose and a preliminary examination of the efficacy of the dose. With twelve patients, if the observed response rate is 33%, the lower bound of a two-sided 90% confidence interval would be 0.12. The maximum width of the 90% CI would be 0.51.

We expect to accrue approximately 25 patients in Part 4. The actual number required will depend upon the observed safety profile, which will determine the number of subjects per dose level, as well as the number of dose escalations required to achieve the MTD or the recommended dose.

8.4 Statistical Methods

The statistical analyses performed for this study will be presented by study phase. For the escalation phase, tabulations will be provided by dose cohort and overall. For the expansion phase, tabulations will be provided by disease cohort and overall. Some analyses may be performed based on the dose escalation and expansion phases combined.

The statistical analyses will be performed using SAS® version 9.2 or later (SAS Institute Inc, Cary NC). Programming specifications will be prepared which describe the datasets and variables created for this study. The datasets will be prepared using the most recent version of CDISC's Study Data Tabulation Model (SDTM) and Analysis Dataset Model (ADaM). The source SDTM and ADaM datasets from which a statistical analysis is performed (including interim safety reviews) will be archived with the Sponsor.

8.4.1 Subject Disposition

The number of subjects included in the safety, PK, pharmacodynamic, and anti-tumor activity analyses will be summarized, along with the reason for exclusion from one or more analysis populations. Subjects discontinuing from study drug and the primary

reason for discontinuation will be summarized. Subjects withdrawing from study and the primary reason for withdrawal will be summarized in a similar manner.

8.4.2 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics for all enrolled subjects will be tabulated by study phase – overall and by dose for Phase 1a (dose escalation/dose finding stage) and overall and by disease cohort for the additional subjects. Each cohort to be presented will be defined in the SAP to provide guidance for the tabulation summaries.

This format of presentation will be used for the safety, efficacy, PK, immune response and biomarker presentations.

8.4.3 Extent of Exposure

The overall duration of study drug administration in weeks will be tabulated for each subject and summarized by study phase. For each subject, the average dose (in mg) of TTI-621 administered and cumulative dose (in mg) administered will be calculated. These data will be further summarized for each cohort by calculating the mean, standard deviation, median, and range of these values. The number and proportion of subjects with one or more dose modifications (i.e., reduction or delay) will be tabulated along with the reason for modification.

8.4.4 Safety Analyses

The SRC, as outlined in Section 3.4, will oversee all safety aspects of the study and make recommendations to the Sponsor.

Safety will be assessed by clinical review of all relevant parameters including AEs, serious adverse events (SAEs), laboratory values, vital signs, ADA, and ECG results. Unless specified otherwise, safety will be analyzed using the Safety Analysis Set defined in Section 8.2. The results of these analyses will be presented by study phase. Some safety analyses, such as ADA, may be performed based on the dose escalation and expansion phases combined.

Summary tables and listings will be provided for all reported treatment-emergent AEs (TEAEs), defined as AEs that start on or after the first administration of study drug. The reported AE term will be assigned a standardized preferred term using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

TEAEs will be summarized based on the number and percentage of subjects experiencing the event by MedDRA System Organ Class and preferred term. As outlined in Section 9.2, the causal relationship between the occurrence of an AE and study drug will be judged by the Investigator. In the event a subject experiences repeat episodes of the same AE, then the event with the highest severity grade and strongest causal relationship to study drug will be used for purposes of incidence tabulations. Tabular summaries will be provided for:

- all TEAEs
- TEAEs by study drug relationship (related, not related) and maximum severity grade
- TEAEs with action of study drug delayed/interrupted or treatment reduced
- TEAEs with action of study drug discontinued
- SAEs

For the escalation phase, the observed DLT rate in each cohort will be calculated by the crude proportion of subjects who experience DLT. Multiple concurrent AEs leading to DLT will be considered a single DLT. The estimate of the DLT rate will be accompanied by a 95% exact binomial confidence interval (CI).

All deaths that occur on study (defined as during treatment or within 30 days of treatment discontinuation) will be reported in a subject listing, which will include the primary cause of death and the number of days between the date of the last dose of study drug and death.

Hematology and serum chemistries will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range for baseline, minimum postbaseline value, maximum postbaseline value, average postbaseline value, and last postbaseline value. Laboratory values will be assigned toxicity grades when available using the NCI CTCAE scale and will be included as AEs if applicable. Directional shifts in laboratory toxicity grades (comparing baseline grade with worst postbaseline grade) will be analyzed using standard shift tables, presenting number and proportion of subjects and their maximum grade shift. Laboratory values taken during the PK sampling may be presented separately if appropriate; the final decision will be recorded in the SAP.

Vital signs will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range in the same manner described for laboratory

values. The results of the 12-lead ECG assessments will be summarized in the same manner as described for laboratories and vital signs.

The incidence, onset time, and titer of ADA will be summarized by descriptive statistics. The possible effects of ADA on PK (such as TTI-621 exposure as measured by C_{max} and AUC after seroconversion), efficacy, and safety of TTI-621 will be explored. Details will be provided in the SAP.

Prior and concomitant medications will be coded to the generic term using the current version of the World Health Organization Drug Dictionary and will be tabulated by cohort and listed by subject.

8.4.5 PK Analyses

The PK of TTI-621 will be estimated from concentration-time data using noncompartmental methods. The reporting of PK parameters will be determined based on the final parameter analysis on the available data. Parameters to be assessed may include, as appropriate, $AUC_{0-\tau}$, $AUC_{0-\infty}$, T_{max}, C_{max}, $t_{1/2}$, clearance, and volume of distribution. CCI [redacted] All final PK analyses will be defined in the final PK analysis plan and/or final SAP as appropriate.

8.4.6 Efficacy Analyses

Efficacy analyses will be conducted using the Full Analysis Set and, where appropriate, the Per-protocol Set; in addition, the overall response rate will also be presented for the Response-Evaluable Set.

The overall response rate will be estimated for each cohort using disease-specific response criteria (see Section 7.14.1). The duration of response (DOR) will be calculated for a subject who achieves a response, and is defined as the number of weeks from the start date of the response (and subsequently confirmed) to the first date recurrent or progressive disease is documented. If a subject dies, irrespective of cause, without documentation of recurrent or progressive disease beforehand, then the date of death will be used to denote the response end date.

Progression-free survival (PFS) is defined as the number of weeks from the date of the first dose of study drug to the earliest of documented recurrent or progressive disease or death due to any cause without prior progression. Leukemia-free survival (LFS) will be calculated in the same manner, as appropriate.

DOR and PFS will be summarized descriptively using the Kaplan-Meier method with 95% CI calculated using Greenwood's formula. Median follow-up for each endpoint will be estimated according to the Kaplan-Meier estimate of potential follow-up. The PFS rate at selected landmarks (e.g., 6 months) and corresponding 95% CIs will be estimated using the Kaplan-Meier method. Greenwood's formula will be used to calculate the standard errors of the Kaplan-Meier estimate and upper and lower limits of the 95% CI.

For DOR and PFS, subjects who meet one or more of the following conditions will be right-censored as follows:

- subjects with no baseline or postbaseline disease assessments unless death occurred prior to the first planned assessment (in which case the death will be considered a PFS event)
- subjects who initiate subsequent anticancer therapy in the absence of documented progression
- subjects who die or have disease progression after missing 2 or more consecutively scheduled disease assessment visits
- subjects who are last known to be alive and progression-free on or before the data cut-off date

For such subjects, the progression or censoring date will be determined based on described conventions (Food and Drug Adminstration, 2007), as outlined in the SAP.

8.4.7 CTCL and PTCL Cohorts

Phase 1b Part 3: CTCL and PTCL Cohorts

Radiographic disease assessments for CTCL and PTCL will be centrally reviewed. Each of the 2 cohorts (CTCL and PTCL) will be evaluated separately for the potential for further study using the Simon 2-stage design. For the first stage, a total of 18 response-evaluable subjects will be reviewed in each cohort; if 2 or fewer responders are observed per cohort, enrollment in that cohort will be terminated. Otherwise, enrollment will proceed to the second stage and an additional 17 response-evaluable subjects will be enrolled per cohort for a total of 35 response-evaluable subjects per cohort. At the end of the second stage, if 6 or fewer responders are observed per cohort, the drug will be rejected for further testing in this indication. If more than the required number of response-evaluable patients are available (i.e., >18 or >35), the first 18 or 35, respectively, would be used.

Phase 1b Part 4: CTCL Cohorts

The subjects enrolled to phase 1b Part 4 will not require submission of scans for central review in real time, but might be requested by sponsor retrospectively.

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9 ADVERSE EVENTS AND SAFETY REPORTING

An AE is any unfavorable medical occurrence in a subject administered investigational product, whether or not thought to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the investigational product. For the purposes of this study, events which are unequivocally due to disease progression should not be reported as AEs. Symptoms of the disease under study/lack of efficacy should not be classified as AEs as long as they are within normal day-to-day fluctuations or expected progression of the disease.

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious AE criteria. New cancers are those that are not the primary reason for administration of study treatment and have been identified after the subject's inclusion in this study. They do not include metastases of the original cancer.

All AEs, complaints, or symptoms that occur from the start of the first dose of study treatment are to be recorded on the appropriate case report form (events ongoing prior to consent are considered medical history unless they worsen during study). Documentation must be supported by an entry in the subject's source medical records. Laboratory abnormalities requiring treatment or considered by the Investigator to be clinically relevant should be reported in the case report form as an AE. Each AE is to be evaluated for duration, severity, and causal relationship with the investigational product.

9.1 Grading and Severity of Adverse Events

The Investigator will grade the severity of each AE using, when applicable, the current version of the CTCAE. In the event of an AE for which no grading scale exists, the Investigator will classify the AE as mild, moderate, severe, life-threatening/debilitating, or fatal, as defined below.

- Mild – An event that is usually transient in nature and generally not interfering with normal activities
- Moderate – An event that is sufficiently discomforting to interfere with normal activities
- Severe – An event that is incapacitating with inability to work or do usual activity, or inability to work or perform normal daily activity
- Life-threatening/debilitating – An event that puts the subject at immediate or potential risk of death, requires hospitalization, or which drastically impacts a subject's well-being

- Fatal

9.2 Adverse Event Attribution

In early human trials, the relationship of an adverse event to the drug is not fully known. Therefore, all AEs should be considered relevant to determining DLT and to reporting unless the event can clearly be determined to be unrelated to the drug. The Investigator will determine whether each AE is considered related to investigational product or not using these categories:

- Related – the time course between administration of investigational product and the occurrence or worsening of the AE is consistent with a possible, likely, or definite causal relationship and no other cause (concomitant drugs or therapies, complications, the primary disease, comorbidities, etc.) can be confirmed
- Unrelated – the time course between the administration of investigational product and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs or therapies, complications, the primary disease, comorbidities, etc.) is confirmed

The following factors should also be considered in the determination of attribution: preclinical pharmacology, PK, and toxicology of the investigational product, whether a particular response is a class effect, concomitant medications, and the primary disease as well as underlying intercurrent conditions.

9.3 Serious Adverse Event Reporting

An SAE is any untoward medical occurrence that, at any dose:

- results in death
- is life-threatening
- requires hospitalization or prolongation of existing hospitalization. Note that some hospitalization scenarios should not be classified as SAEs, including (1) those that are related to performance of an efficacy measurement for the study, (2) diagnostic or elective surgical procedures for a pre-existing medical condition that has not changed and (3) scheduled therapy for the target disease under evaluation
- results in disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event in the view of the Investigator

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

All SAEs must be reported to the Sponsor's representative within 24 hours of knowledge:

Tel: (615) 329-7358
Fax: (866) 807-4325
Email: CANN.SAE@scri-innovations.com

To report the SAE, the completed report form will be sent to the Sponsor's clinical safety representative within 24 hours of awareness. Incoming reports are reviewed during normal business hours. Additional reporting instructions and the Serious AE Report Form may be found in the Study Manual.

The Investigator will be requested to supply detailed information regarding the event. SAEs must also be reported to the Institutional Review Board (IRB) or Ethics Committee (EC) and a copy of that report must be retained at the investigative site and filed in the Investigator Site File in accordance with the requirements of that institution.

If a subject becomes pregnant while enrolled in the study or within 60 days after last dose, a Pregnancy Form should be completed and submitted to the Sponsor within 24 hours of the information being available, irrespective of whether or not it meets the criteria for expedited reporting. The Sponsor must be notified of any subject's partner who becomes pregnant during the study or within 60 days after last dose. To capture information about a pregnancy from the partner of a male subject, the consent of the male subject's partner must be obtained to collect information related to the pregnancy and outcome; the male subject should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring should be followed and documented. If the pregnancy continues to term, details regarding the birth and health of the baby will be documented.

9.4 Reporting Periods for Adverse Events and Serious Adverse Events

All AEs regardless of seriousness or relationship to TTI-621 treatment that occur from the start of the first dose of study treatment until the safety follow-up visit (i.e., 30 days after the last study treatment) are to be recorded on the corresponding case report form (CRF). All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All AEs that occur during the reporting period must be recorded and followed until resolution unless, in the opinion of the investigator, the AE or laboratory

abnormality/ies are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the subject's medical record and as a comment on the CRF. After 30 days following the last dose of study treatment, only AEs assessed by the investigator as treatment related or AEs of special interest are to be reported for a period of 1 year following the safety follow-up visit. Any SAE that is considered to be related to study treatment should be reported to the Sponsor at any time regardless of last treatment dose. If the study is closed at the time of the SAE, the SAE should be reported to drugsafety@trilliumtherapeutics.com.

9.5 Adverse Events of Special Interest

In the escalation phase of the study, Investigators should report to the Medical Monitor within 24 hours all clinically significant incidences of the AEs of special interest listed below, which are based on preclinical toxicology findings, theoretical mechanistic considerations, or clinical experience with TTI-621 to-date. Additional details are provided in the Investigator's Brochure.

Thrombocytopenia
Thrombocytopenia is an important, identified risk for TTI-621. Transient decreases in platelets without clinical sequelae occurred in the 24 hours following infusion in the majority of subjects exposed to IV administered TTI-621. Overall 47/179 subjects (26%) who received IV TTI-621 in Study TTI-621-01 had AEs of thrombocytopenia/platelet count decreased. These findings were consistent with augmented systemic phagocytic clearance of platelets. Platelet counts returned to baseline levels within 1 week, enabling continued weekly dosing. No increased risk of bleeding was observed. Subjects participating in the clinical trials have frequent hematology assessments to monitor for potential thrombocytopenia. In addition, study protocols require dose delays or reductions in the event of Grade 3 or higher thrombocytopenia and allow use of megakaryopoiesis-stimulating agents and blood products to treat thrombocytopenia as needed.

Hemorrhage
Hemorrhage is considered a potential important risk for TTI-621. A total of 24/179 subjects (13%) in Study TTI-621-01 experienced 1 or more hemorrhage/bleeding events. Overall, 20/179 subjects (11%) experienced Grade 1 or 2 events and 4 subjects (2%) had Grade 3 events. Grade 3 hemorrhage events were considered treatment-related for 3 subjects (2%). No Grade 4 hemorrhage events were reported. One subject had 2 SAEs of gastrointestinal hemorrhage; the subject had a history of prior hemorrhage from a disease site. Subjects participating in the clinical trials will continue to be closely monitored for hemorrhage, changes in platelet counts and coagulation factors.

Other Cytopenias

Other cytopenias are considered potential risks for TTI-621 and are not considered to be important risks. The incidence of treatment-emergent cytopenias (monocytes, neutrophils, and lymphocytes) was relatively low and consistent with that reported for patients with the diseases under study, including advanced hematologic malignancies.

Infusion-Related Reactions

Infusion- and injection site-related reactions are important, identified risk for TTI-621. The majority of subjects exposed to TTI-621 experienced mild-to-moderate infusion- or injection site-related reactions. Symptoms of infusion-related reactions include chills, fever, rash, urticaria, dyspnea, hypotension, and/or nausea/vomiting. Symptoms of injection site-related reactions, include injection site pain, bruising, erythema, and pruritus. The study protocols mandate that all subjects must be premedicated with an antihistamine and acetaminophen prior to TTI-621 administration. In addition, subjects will continue to be followed closely for the development of ADA in accordance with the schedule of assessments in the study protocols, as well as for infusion- and injection site-related reactions.

Anemia

Anemia is considered a potential risk for TTI-621 and is not considered to be an important risk. Treatment-related, Grade 3 anemia was reported in subjects receiving IV TTI-621. The overall incidence was consistent with that reported for patients with advanced hematologic malignancies and transfusion-dependence. In addition, events most frequently occurred in subjects with primary hematologic malignancies in which anemia is frequently caused by the malignancy itself (AML, MDS, MM, and advanced HL). No serious events of anemia were reported and anemia did not appear to be associated with increased destruction of erythrocytes. Anemia was not observed in subjects receiving intratumoral TTI-621.

ALT/AST Elevations

ALT/AST elevations are considered potential risks for TTI-621 and are not considered to be important risks. Increased ALT and AST were observed in toxicology study in cynomolgus monkeys, in association with increased total and direct bilirubin. Transaminase increases have been infrequently reported as TEAEs on Study TTI-621-01; 5/179 subjects (3%) had ALT and AST elevations, and 1 additional subject (1%) was reported with an AST increase. The maximum severity ALT/AST increase was Grade 1–2 for 3 subjects, and Grade 3–4 for 3 subjects; none of these events were reported as SAEs. Liver enzymes of subjects participating in the clinical trials should continue to be monitored closely during treatment.

Other

Although the individual components of the TTI-621 fusion protein are human, the juncture between the components may be sensed as foreign by the immune system. Therefore, as with other biological therapeutics, the potential exists for the emergence of ADA. Although the Investigators cannot assess the development of ADA directly, serial samples will be taken throughout the exposure period to measure ADA.

10 ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory Authority Approval

This study will be conducted in accordance with applicable national and local regulations and guidelines, Good Clinical Practice (GCP)-International Conference on Harmonisation (ICH) guidelines (Integrated Addendum To ICH E6(R1): Guideline For Good Clinical Practice, E6(R2), Current Step 4 version (2016), the National Statement on Ethical Conduct in Human Research 2007, and The Declaration of Helsinki (Brazil, 2013).

10.2 Ethics Approval

Prior to initiation of the study, the Investigator will submit the study protocol, Informed Consent, and any other document that may be requested by the designated IRB/EC for review and approval. The Investigator will request that the IRB/EC provide written approval of the study and will keep on file records of approval of all documents pertaining to this study.

The IRB/EC will be notified of any amendments to the protocol. With the exception of any amendment that is imperative to the protection of subject safety, protocol amendments require approval by the IRB/EC prior to being implemented by the site.

10.3 Informed Consent and Protected Health Information

Written informed consent and authorization of use and disclosure of protected health information must be obtained from each subject (or the subject's legal representative) prior to performing any study evaluation. The authorization for use and disclosure of protected health information must contain the elements required by 45 CFR 164.508(b) for valid authorizations. The proposed informed consent form, which must be in compliance with regulatory regulations, must have been reviewed and approved by the Sponsor and the study IRB/EC prior to initiation of the study. The proposed informed consent form should contain the 20 elements of the informed consent described in ICH E6 4.8. These requirements are in accordance the Code of Federal Regulations (21 CFR 50.25) and the Declaration of Helsinki.

Each subject will be given a copy of the signed Informed Consent Form. The source documents for each subject shall document that the Informed Consent was obtained prior to participation. The subjects will also be instructed that they are free to withdraw their consent and discontinue their participation in the study at any time without prejudice. Prior

to the start of the study, the Principal Investigator will provide the Sponsor with an actual Informed Consent Form approved by the IRB/EC for use during the study.

Any amendments to the Informed Consent Form must be approved by the Sponsor and the IRB/EC. Consent will be verified and countersigned by the Principal Investigator or designee. The sample Informed Consent prepared by the Sponsor may be found in the Study Manual.

10.4 Clinical Supplies

The Principal Investigator will be responsible for the dispensing, inventory, and accountability of all clinical supplies, ensuring that accepted medical and pharmaceutical practices are followed. An accurate and timely accountability record of the disposition of all clinical supplies must be maintained. The supplies and inventory record must be made available for inspection by the Sponsor or the designated Sponsor's representative upon request. Under no circumstances will the Principal Investigator allow the investigational product to be used other than as directed by this protocol.

Additional accountability procedures are fully outlined in the Study Manual.

10.5 Data Management and Study Monitoring

Data will be recorded at the site on source documents and reviewed by the Sponsor's monitor during periodic visits, who will verify data recorded in the case report forms with source documents. Additional instructions may be found in the Study Manual.

The Sponsor or its representatives will periodically visit the clinical site during the conduct of the study in accordance with applicable regulations and GCP. These activities will be done in order to verify that the data are authentic, accurate, and complete; that the safety and rights of the subject are being protected; and that the study is conducted in accordance with the currently approved protocol, GCP, and all applicable regulatory requirements. Additional instructions are outlined in the Study Manual.

10.6 Records Retention

The Principal Investigator will retain copies of the approved protocol, completed case report forms, informed consent documents, relevant source documents, and all other supporting documentation related to the project for a period of at least 2 years after the last approval of a marketing application for TTI-621 in an ICH region or at least 2 years after the formal discontinuation of the clinical development of the investigational product. However, for some regulatory agencies, documentation may be required to be maintained

for up to 25 years. In order to ensure that regulatory requirements are met, the Principal Investigator agrees that copies of study records will be retained until the Sponsor's written agreement for disposal has been obtained.

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12 APPENDICES

Appendix A. Definitions of Indolent vs Aggressive B-cell Lymphomas and T cell lymphomas*

Indolent B-cell lymphoma (IBCL)

- Follicular lymphoma (follicular small-cleaved cell [grade 1], follicular mixed small-cleaved and large cell [grade 2], and diffuse small-cleaved cell)
- Extranodal marginal zone B-cell lymphoma (MALT lymphoma)
- Nodal marginal zone B-cell lymphoma (monocytoid B-cell lymphoma)
- Splenic marginal zone lymphoma (splenic lymphoma with villous lymphocytes)
- Cutaneous B-cell lymphoma

Aggressive B-cell lymphoma (ABCL)

- Diffuse large cell lymphoma (includes diffuse mixed-cell, diffuse large cell, immunoblastic, and T-cell rich large B-cell lymphoma)
- Precursor B-cell lymphoblastic lymphoma
- Mantle cell lymphoma
- True histiocytic lymphoma
- Primary effusion lymphoma
- Burkitt lymphoma
- Transformed lymphoma
- Primary mediastinal B-cell lymphoma (PMBL)

Cutaneous T-cell lymphoma

- Mycosis fungoides with and without transformation
- Sézary syndrome

Peripheral T-cell lymphoma

- Adult T-cell leukemia/lymphoma
- Extranodal NK-/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Hepatosplenic T-cell lymphoma

- Subcutaneous panniculitis-like T-cell lymphoma
- Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma delta+ T-cell lymphoma
- Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
- Primary cutaneous acral CD8+ T-cell lymphoma
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma
- Nodal peripheral T-cell lymphoma with TFH phenotype
- Anaplastic large-cell lymphoma, ALK+
- Anaplastic large-cell lymphoma, ALK-
- Breast implant–associated anaplastic large-cell lymphoma

* This list is representative and is not intended to be exhaustive/include all types of indolent or aggressive B-cell or T-cell lymphomas that may be enrolled on study

Appendix B. Eastern Cooperative Oncology Group Performance Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities, up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: (Oken et al., 1982)

Appendix C. Grading Scale for Skin Symptoms of Graft-vs-host Disease

	0	1	2	3	4
Acute	No rash due to GVHD	Maculopapular rash < 25% of body surface	Maculopapular rash 25–50% of body surface	Maculopapular rash > 50% of body surface	Generalized erythroderma with bullous formation
Chronic [a]	No symptoms	< 18% BSA with disease signs but no sclerotic features	19–50% BSA or involvement with superficial sclerotic features (able to pinch)	> 50% BSA or deep sclerotic features (unable to pinch) or impaired mobility, ulceration, or severe pruritus	-

[a] Clinical features may include maculopapular rash, lichen planus-like features, papulosquamous lesion or ichthyosis, hyper- or hypopigmentation, keratosis pilaris, erythema, erythroderma, poikiloderma, sclerotic features, pruritus, hair involvement, nail involvement

BSA = body surface area; GVHD = graft-vs-host-disease

Appendix D. Summary of Tests and Observations

Appendix D. Table 1. Phase 1b - Part 2 and 3: Schedule of Assessments (additional assessments as clinically indicated)

Assessments	≤ -D14	W1 D1 Pre[a]	W1 D1 Post	W2 D1	W3 D1	W4 D1	W5 D1	W6 D1	W7 D1	W8 D1 Pre	W8 D1 Post	W9 + D1	Intra Sub Dose[g] Intens	EOT	SFU[e]	LTFU
		Except where otherwise noted these visit pre-dose assessments can be performed up to 24 hours pre-infusion (see also Section 7). All scheduled treatment days have a window of ± 2 days												≤1 Wk[j]	±2D	Q4 (±1 wk)
Informed consent (within 30 days)	X															
Medical, malignancy history	X															
Physical exam[b], ECOG	X	pre[b]		pre[b]	pre[b]	pre[b]				pre[b]		pre[b] Wk 12 then Q4 wks		X	X[b]	
Body weight	X	pre		pre	pre	pre	pre	pre	pre	pre		pre Wk 10 + Q2 wks [q]		X	X	
Vital signs[c] *** Combo arms** – done for both infusions if >1 hr apart	X	*pre	(*1 hr [EOI]), 2 hr, 4 hr	* pre, 1hr (EOI)	* pre, 1 hr (EOI)	* pre, 1 hr (EOI)	pre	pre	pre	pre	pre	pre		X	X	
Disease assessment (incl. photographs)[d]	X[k]										post	post Wk16, 24 +Q12 wks[o]		X[i]		
12-lead ECG	X	pre	post [m]							pre		pre on Wk16 & 24		X		
QOL by FACT-G (all subjects), SKINDX29 (CTCL only)	X										post	post Wk16, 24 + Q12 wks		X		
TTI-621 infusion[s]		X		X	X	X	X	X	X	X		X				
AEs		X		X	X	X	X	X	X	X	X	X	X	X	X	X (TEAE)
Prior/concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X	X		
Survival Status																X
Subsequent anticancer therapies																X
	D = Day; Post = after start of TTI-621 infusion, EOT = end of treatment visit; SFU = safety follow-up visit; LTFU = long term safety follow-up visit; EOI = end of infusion (1 hr)															

Assessments	≤ -D14	W1 D1 Pre[a]	W1 D1 Post	W2 D1	W3 D1	W4 D1	W5 D1	W6 D1	W7 D1	W8 D1 Pre	W8 D1 Post	W9 + D1	Intra Sub Dose[g] Intens	EOT	SFU[e]	LTFU
					Dose Intensification Weeks for phase 1b Part 3 (see Section 6.5.4)											
		Except where otherwise noted the visit pre-dose assessments can be performed up to 24 hours pre-infusion (see also Section 7). All scheduled treatment days have a window of ± 2 days												≤1 Wk[j]	± 2D	Q4 (±1 wk)
	Local Laboratory Assessments															
Hepatitis B/C panel	X															
Pregnancy test (women of childbearing potential)	X (serum)					pre (serum or urine)				pre (serum or urine)		pre Wk 12 then Q4 wks (serum or urine)				
Hematology	X	pre	1 hr, (EOI) 2 hr, 4 hr	pre	pre	pre	pre	pre	pre	pre		pre	4 hr	X	X	
		WBC with automated 5-part differential, hemoglobin, RBC, absolute reticulocytes, platelets														
Serum chemistries	X	pre		pre	pre	pre				pre		pre Wk 12 then Q4 wks	4 hr	X	X	
		Alkaline phosphatase, albumin, ALT, AST, bilirubin (direct, indirect, and total), BUN, creatinine, glucose, LDH, total protein, uric acid, and electrolytes (sodium, potassium, calcium, chloride, bicarbonate, phosphorus)														
TSH **(for Nivolumab combination only)**	X											pre Wk12 + Q12 wks		X	X	
Coagulation panel	X													X		
		Prothrombin time, partial thromboplastin time, INR, fibrinogen														
Urinalysis		pre								pre				X		
		Including color, appearance, specific gravity, pH, glucose, bilirubin, ketones, occult blood, and protein														
	D = Day; Post = after start of TTI-621 infusion; EOT = end of treatment visit; SFU = safety follow-up visit; LTFU = long term safety follow-up visit; EOI = end of infusion (1 hr)															

Assessments	**≤ -D14**	**W1 D 1 Pre[a]**	**W1 D1 Post**	**W2 D1**	**W3 D1**	**W4 D1**	**W5 D1**	**W6 D1**	**W7 D1**	**W8 D1 Pre**	**W8 D1 Post**	**W9 + D1**	**Intra Sub Dose[g] Intens**	**EOT**	**SFU[e]**	**LTFU**
					Dose Intensification Weeks for phase 1b Part 3 (see Section 6.5.4)											
		Except where otherwise noted pre-dose assessments can be performed up to 24 hours pre-infusion (see also Section 7). All scheduled treatment days have a window of ±2 days.												≤1 Wk[j]	± 2D	Q4 (±1 wk)
	Central Laboratory Assessments															
PK		pre	1 hr (EOI) 2hr, 4hr, D2	pre	pre	pre	pre	pre	pre	pre	1 hr (EOI) 2 hr, 4 hr D2, D4	pre Wk 9, 10, 11, 12, 13, 14, 15 & 16	1 hr (EOI), 4 hr	X		
Cyto/Chemokine		pre	1 hr (EOI) 4 hr	pre						pre	1 hr (EOI), 4 hr, D2	pre Wk 9		X		
ADA		pre				pre				pre		pre Wk 12 then Q4 wks		X	X	X[f]
TCR Vβ[p]		pre								pre		pre Wk 16				
Anti-Tumor Antibodies		pre										pre Wk 16				
Peripheral Receptor Occupancy **(blood)**[l]		pre	1 hr (EOI)	pre						pre	1 hr (EOI)	pre Wk 9	pre, 1 hr (EOI)			
Receptor Occupancy (bone marrow)[p]	pre[n]									pre[n]						
Innate and Adaptive Response Assay		pre								pre				X		
Tissue for biomarkers[p]	X[h]									pre[p] CTCL O: all other diagnoses		pre[p] Wk 16 (CTCL)				
Tissue for central pathology	X[r]															
D = Day; Post = after start of TTI-621 infusion; EOT = end of treatment visit; SFU = safety follow-up visit; LTFU = long term safety follow-up visit; O = optional, EOI = end of infusion (1 hr)																

Footnotes

[a] Screening laboratories may be used as pre-dose baseline if within 3 days of Day 1

[b] Review of systems and physical exam: breast/chest, extremities, head/ears/eyes/nose/throat, lymph nodes, musculoskeletal, pulmonary, skin, height. Symptom driven on all treatment weeks and SFU. Full exam at screening and EOT.

[c] Including heart rate, respiratory rate, body temperature.

[d] See Appendix D. Table 3 and Section 7.14.1 for further details, including disease assessment scales. For CTCL and PTCL subjects, central submission of radiographic disease assessment is required. Also for CTCL subjects only: mSWAT, CAILS (if applicable) and photographs. All response assessments should be performed at the end of the indicated weeks and the time points have a window of ±1 week.

[e] If treatment-emergent abnormalities are present at end of treatment, repeat pertinent labs or studies

[f] Subjects who are seropositive at end of safety follow-up should be monitored at least quarterly for 1 year post study to assess persistence of antibodies.

[g] If not already included in the regular scheduled visit assessment, these are to be performed for dose-intensified subjects in addition to the regularly scheduled visit assessments. Dose intensification to occur from Week 3 to Week 8. After Week 9, additional dose intensification is not permitted.

[h] For subjects with SS, peripheral blood is acceptable, if a biopsy is not possible. For all other subjects fresh tumor biopsy required if feasible. Archival tissue at screening acceptable, if biopsy not feasible.

[i] If not done in prior 8 weeks

[j] Within 1 week following the final dose of TTI-621 (or at the time of premature discontinuation of treatment)

[k] Within 28 days of planned start of treatment

[l] Blood for peripheral receptor occupancy to be drawn pre-infusion and 1 hr post-infusion (EOI) at each dose-intensification and at Week 8

[m] 12-lead ECG within approximately 30 minutes of completion of infusion (i.e., 60–90 minutes after Time 0)

[n] For subjects with marrow based disease only, at time of disease assessments

[o] Or at the time of observed or suspected clinical progression

[p] ±1 week to align with response assessments

[q] After Week 8, the weight taken at the prior visit may be used to calculate dose (e.g. weight at Week 8 used for Week 9 dosing)

[r] Tumor tissue will be submitted for central review for subjects with CTCL (not including Sezary Syndrome) and PTCL. For Sezary Syndrome patients, peripheral blood and blood smears are required at screening, all response assessment time points and at end of treatment (See Appendix D. Table 3). Central disease confirmation not required for enrollment.

[s] For patients who have been given weekly infusion of TTI-621 for more than a year and are receiving clinical benefit (objective response or clinically meaningful long-term stable disease), investigators may exercise their discretion to reduce the dosing frequency from weekly to bi-weekly following the discussion and approval from the sponsor or designees.

Appendix D. Table 2. Phase 1b - Part 4 Dose Optimization: Schedule of Assessments

Assessments	≤ -D14	W1[a]	W2 D1	W3 D1	W4 D1	W5 D1	W6 D1	W7 D1	W8 D1	W9 + D1	EOT	SFU[e]	LTFU
		DLT evaluation Period											
		Except where otherwise noted these visit pre-dose assessments can be performed up to 24 hours pre-infusion (see also Section 7). All scheduled treatment days have a window of ± 2 days									≤1 Wk [h]	±2D	Q4 (±1 wk)
Informed consent (within 30 days)	X												
Medical, malignancy history	X												
Physical exam[b], ECOG	X	pre[m]	pre[m]	pre[m]	pre[m]	pre[m]	pre[m]	pre[m]	pre[m]	pre[m]	X	X[m]	
Body weight	X	pre	pre	pre	pre	pre	pre	pre	pre	pre Wk 10 + Q2 wks[l]	X	X	
Vital signs[c]	X	pre, (1 hr [EOI]), 2 hr, 4 hr	pre	pre	pre	pre	pre	pre	pre	pre	X	X	
Disease assessment (incl. photographs)[d]	X[i]								post	post Wk16, 24 +Q12 wks [k]	X[g]		
12-lead ECG	X	pre and post[j]			pre				pre	pre Wk12 + Q4 weeks	X		
QOL by FACT-G, SKINDX29	X								post	post Wk16, 24 +Q12 wks [k]	X		
TTI-621 infusion[s]		X	X	X	X	X	X	X	X	X			
AEs		X	X	X	X	X	X	X	X	X	X	X	X (TEAE)
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X		
Survival Status													X
Subsequent anticancer therapies													X

D = Day; Post = after start of TTI-621 infusion, EOT = end of treatment visit; SFU = safety follow-up visit; LTFU = long term safety follow-up visit; EOI = end of infusion (1 hr)

Assessments	≤ -D14	W1[a]	W2 D1	W3 D1	W4 D1	W5 D1	W6 D1	W7 D1	W8 D1	W9 + D1	EOT	SFU[e]	LTFU
		DLT Evaluation Period											
		Except where otherwise noted the visit pre-dose assessments can be performed up to 24 hours pre-infusion (see also Section 7). All scheduled treatment days have a window of ± 2 days									≤1 Wk [h]	± 2D	Q4 (±1 wk)
Local Laboratory Assessments													
Hepatitis B/C panel	X												
Pregnancy test (women of childbearing potential)	X (serum)				pre (serum or urine)				pre (serum or urine)	pre Wk 12 then Q4 wks (serum or urine)			
Hematology [n]	X	pre, 1 hr, (EOI), 2 hr, 4 hr D2, D4	pre, 4 hr, (D2[n*] if clinically indicated)	pre, 4 hr, (D2[n*] if clinically indicated)	pre	pre	pre	pre	pre	pre	X	X	
		WBC with automated 5-part differential, hemoglobin, RBC, absolute reticulocytes, platelets											
Serum chemistries	X	pre	pre	pre	pre				pre	pre Wk 12 then Q4 wks	X	X	
		Alkaline phosphatase, albumin, ALT, AST, bilirubin (direct, indirect, and total), BUN, creatinine, glucose, LDH, total protein, uric acid, and electrolytes (sodium, potassium, calcium, chloride, bicarbonate, phosphorus)											
Coagulation panel	X	pre	pre	pre	pre				pre	pre Wk 12, W16 then Q4 wks [P]	X		
		Prothrombin time, partial thromboplastin time, INR, fibrinogen											
Urinalysis		pre									X		
		Including color, appearance, specific gravity, pH, glucose, bilirubin, ketones, occult blood, and protein											
D = Day; Post = after start of TTI-621 infusion; EOT = end of treatment visit; SFU = safety follow-up visit; LTFU = long term safety follow-up visit; EOI = end of infusion (1 hr)													

Assessments	≤ -D14	W1[a]	W2 D1	W3 D1	W4 D1	W5 D1	W6	W7 D1	W8 D1	W9 + D1	EOT	SFU[e]	LTFU
		DLT Evaluation Period											
		Except where otherwise noted pre-dose assessments can be performed up to 24 hours pre-infusion (see also Section 7). All scheduled treatment days have a window of ±2 days.									≤1 Wk [h]	± 2D	Q4 (±1 wk)
Central Laboratory Assessments													
PK[o]		pre 1 hr (EOI) 2hr, 4hr, D2, D4	pre	pre	pre	pre	pre, 1 hr (EOI) 2 hr, 4 hr D2,D4	pre	pre	pre Wk 9, 10, 11, 12, 13, 14, 15 & 16	X		
ADA		pre			pre				pre	pre Wk 12 then Q4 wks	X	X	X[f]
Peripheral Receptor Occupancy **(blood)** [q]		pre, 1 hr (EOI)	pre				pre, 1 hr (EOI)	pre		pre Wk 12 and 16			
Tissue for biomarkers [r]	X								pre	pre Wk 16			
D = Day; Post = after start of TTI-621 infusion; EOT = end of treatment visit; SFU = safety follow-up visit; LTFU = long term safety follow-up visit; O = optional, EOI = end of infusion (1 hr)													

Footnotes

[a] Screening laboratories may be used as pre-dose baseline if within 3 days of Day 1
[b] Review of systems and physical exam: breast/chest, extremities, head/ears/eyes/nose/throat, lymph nodes, musculoskeletal, pulmonary, skin, height. Symptom driven on all treatment weeks and SFU. Full exam at screening and EOT.
[c] Including heart rate, respiratory rate, body temperature.
[d] See Appendix D. Table 3 and Section 7.14.1 for further details, including disease assessment scales. mSWAT, CAILS (if applicable) and photographs are required. All response assessments should be performed at the end of the indicated weeks and the time points have a window of ±1 week. The subjects enrolled to phase 1b Part 4 cohorts will not require submission of scans for central review in real time but retrospective submissions might be requested by sponsor.
[e] If treatment-emergent abnormalities are present at end of treatment, repeat pertinent labs or studies
[f] Subjects who are seropositive at end of safety follow-up should be monitored at least quarterly for 1 year post study to assess persistence of antibodies.
[g] If not done in prior 8 weeks
[h] Within 1 week following the final dose of TTI-621 (or at the time of premature discontinuation of treatment)
[i] Within 28 days of planned start of treatment
[j] 12-lead ECG within approximately 30 minutes of completion of infusion (i.e., 60–90 minutes after Time 0)
[k] Or at the time of observed or suspected clinical progression
[l] After Week 8, the weight taken at the prior visit may be used to calculate dose (e.g. weight at Week 8 used for Week 9 dosing)
[m] Symptom driven physical examination
[n] Hematology: *The week 2 and week 3 day 2 assessments are only required if clinically indicated in the event that ≥ Grade 4 thrombocytopenia is observed on day 1 or there are any other clinical conditions indicated for a follow-up lab assessment at the investigator discretion. If a priming regimen is required, refer to Appendix F.
[o] PK: if a priming regimen is required, refer to Appendix F
[p] Symptom driven coagulation panel from week 16 onward

[q] Peripheral Receptor Occupancy (blood): if a priming regimen is required, refer to Appendix F
[r] Fresh tumor biopsy required if feasible. Peripheral blood is acceptable for subjects with SS. Archival tissue at screening acceptable, if biopsy not feasible.
[s] For patients who have been given weekly infusion of TTI-621 for more than a year and are receiving clinical benefit (objective response or clinically meaningful long-term stable disease), investigators may exercise their discretion to reduce the dosing frequency from weekly to bi-weekly following the discussion and approval from the sponsor or designees.

Appendix D. Table 3. Response Assessments by Malignancy Type

Radiographic disease assessments for CTCL and PTCL will be submitted for central review for those subjects enrolled to phase 1b Part 3. The subjects enrolled to phase 1b Part 4 cohorts will not require submission of scans for central review in real time but retrospective submissions might be requested by sponsor.

Central photography will be utilized for CTCL patients for both phase 1b Part 3 and Part 4.

Disease and Assessments	Screening	Wk 8 [l]	Wk 12 [l]	Wk 16 [l] +	EOT
Lymphoma (including PTCL)					
PET/CT scan (PTCL: local and central review for phase 1b Part 3 only)	X	X		Weeks 16, 24, and every 12 weeks thereafter	X
Spleen assessment	X	X		Weeks 16, 24, and every 12 weeks thereafter	X
Bone marrow biopsy [a]	X	X		Weeks 16, 24, and every 12 weeks thereafter	X
Cutaneous T-Cell Lymphoma					
Skin assessment (mSWAT and CAILS)	X	X		Weeks 16, 24, and every 12 weeks thereafter	X
Radiographic imaging (central for CTCL for phase 1b Part 3 only)[b]	X	X		Weeks 16, 24, and every 12 weeks thereafter	X
Photography of disease (central for CTCL for phase 1b Part 3 and Part 4)[k]	X	X		Weeks 16, 24, and every 12 weeks thereafter	X
Blood assessment (pathology and flow cytometry): local and central (CTCL) for phase 1b Part 3 only [c]	X	X		Weeks 16, 24, and every 12 weeks thereafter	X
Spleen and liver assessment	X	X		Weeks 16, 24, and every 12 weeks thereafter	X
Acute Leukemia (AML and ALL)					
Bone marrow aspirate or biopsy [d]	X	X		Weeks 16, 24, and every 12 weeks thereafter	X
Cytogenetic evaluation [e]	X	X		Weeks 16, 24, and every 12 weeks thereafter	X
Molecular and/or flow cytometric evaluation [f]	X	X		Weeks 16, 24, and every 12 weeks thereafter	X
Myelodysplastic Syndrome [g]					
Bone marrow biopsy	X	X		Week 16, 24, and every 12 weeks thereafter	X
Peripheral blood (including blasts)	X	X		Week 16, 24, and every 12 weeks thereafter	X
Cytogenetic evaluation [h]	X	X		Week 16, 24, and every 12 weeks thereafter	X
MDS/MPN Overlap (including CMML)					

Disease and Assessments	Screening	Wk 8 [l]	Wk 12 [l]	Wk 16 [l] +	EOT
Bone marrow biopsy	X	X		Week 16, 24, and every 12 weeks thereafter	X
Peripheral blood (including blasts and neutrophil precursors)	X	X		Week 16, 24, and every 12 weeks thereafter	X
Spleen and liver assessment	X	X		Week 16, 24, and every 12 weeks thereafter	X
Cytogenetic evaluation [h]	X	X		Week 16, 24, and every 12 weeks thereafter	X
Myelofibrosis [i]					
Bone marrow biopsy	X		X	Week 24 and every 12 weeks thereafter	X
Peripheral blood (including immature myeloid cells)	X		X	Week 24 and every 12 weeks thereafter	X
Spleen and liver assessment	X		X	Week 24 and every 12 weeks thereafter	X
Essential Thrombocythemia and Polycythemia Vera (ET, PV) [i]					
Bone marrow biopsy	X		X	Week 24 and every 12 weeks thereafter	X
Spleen and liver assessment	X		X	Week 24 and every 12 weeks thereafter	X
Small Cell Lung Cancer					
Radiographic imaging [j]	X	X		Week 16 and every 8 weeks thereafter	X

[a] A bone marrow biopsy for lymphomas should be completed if clinically indicated.
[b] Radiographic imaging should only be performed if visceral lesions were identified at screening and to confirm a response after screening and submitted for central review.
[c] The blood assessment includes Sézary cell counts and/or flow cytometry for CD4/CD8, CD4+ CD7-, or CD4+ CD26- cells. Blood and pathology submitted for central review
[d] A bone marrow aspirate or biopsy is required to establish CR, CRi, PR or relapse per IWG Criteria (Cheson et al, 2003). A bone marrow evaluation is also required when the peripheral blood has < 10% peripheral leukemic blasts.
[e] In order to document a cytogenetic complete remission (CRc), reversion to a normal karyotype must occur; cytogenetics not necessary if normal karyotype.
[f] In the event of a CR, real-time quantitative PCR (RT-PCR) and flow cytometry should be performed to monitor minimal residual disease (MRD) and to document molecular complete remission (CRm); for subjects in CR, consult with Medical Monitor to review specific tests indicated.
[g] All criteria must be met and documented for a minimum of 4 weeks to define a complete remission, partial remission, or marrow CR.
[h] At least 20 analyzable metaphases are required to diagnose or exclude the presence of a cytogenetic abnormality; for subjects in CR, consult with Medical Monitor to review specific tests indicated.
[i] To confirm a response, all criteria must be met and documented for a minimum of 12 weeks; for subjects in CR, consult with Medical Monitor to review specific tests indicated.
[j] CT scans of the chest, abdomen, and pelvis should be conducted every 8 weeks. CT/MRI of the brain should be performed if abnormal at baseline
[k] Canfield photography of target lesions should be conducted and submitted for central storage
[l] All time points are relative to the end of the respective weeks (ie. end of week 8)

Appendix E. Cockcroft-Gault Equation for Calculating Estimated Creatinine Clearance

Serum creatinine units	Gender	Estimated Creatinine Clearance (mL/min)
mg/dL	Male	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)}}{72 \times \text{subject serum creatinine (mg/dL)}}$
	Female	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 0.85}{72 \times \text{subject serum creatinine (mg/dL)}}$
µM/dL	Male	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 1.23}{\text{Subject serum creatinine (µM/dL)}}$
	Female	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 1.04}{\text{Subject serum creatinine (µM/dL)}}$

Appendix F. Expansion Phase 1b Part 4 Dose Regimen Scenarios for Hematology, PK and Receptor Occupancy (blood)

Sample Collection at Weeks 1 – 7 for Cohorts With Priming Regimens

Example: Sample Collections for Cohorts With Priming (first highest stable dose at week 2, priming for 1 week)

Assessment	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7
Dose	Priming Dose*	Highest Stable Dose					
Hematology	Pre, 4 hr	Pre, 1 hr (EOI), 2hr, 4hr, D2, D4	Pre, 4 hr, ***D2	Pre	Pre	Pre	Pre
PK	Pre, 1 hr (EOI)	Pre, 1 hr (EOI), 2hr, 4hr, D2, D4	Pre	Pre	Pre	**Pre, 1 hr (EOI), 2hr, 4hr, D2, D4	Pre
Receptor Occupancy (blood)	Pre, 1 hr (EOI)	Pre, 1 hr (EOI)	Pre			**Pre, 1 hr (EOI)	Pre

* Priming regimens with more than 1 priming week will follow the same pattern as included for Week 1, whereby additional priming dose weeks will be added with the same sampling timepoints for hematology, PK and receptor occupancy (blood) as at week 1.

** The PK and receptor occupancy serial samples will remain at week 6 irrespective of the number of priming weeks

*** The day 2 assessments are only required if clinically indicated in the event that ≥ Grade 4 thrombocytopenia is observed on day 1 or there are any other clinical conditions indicated for a follow-up lab at the investigator discretion

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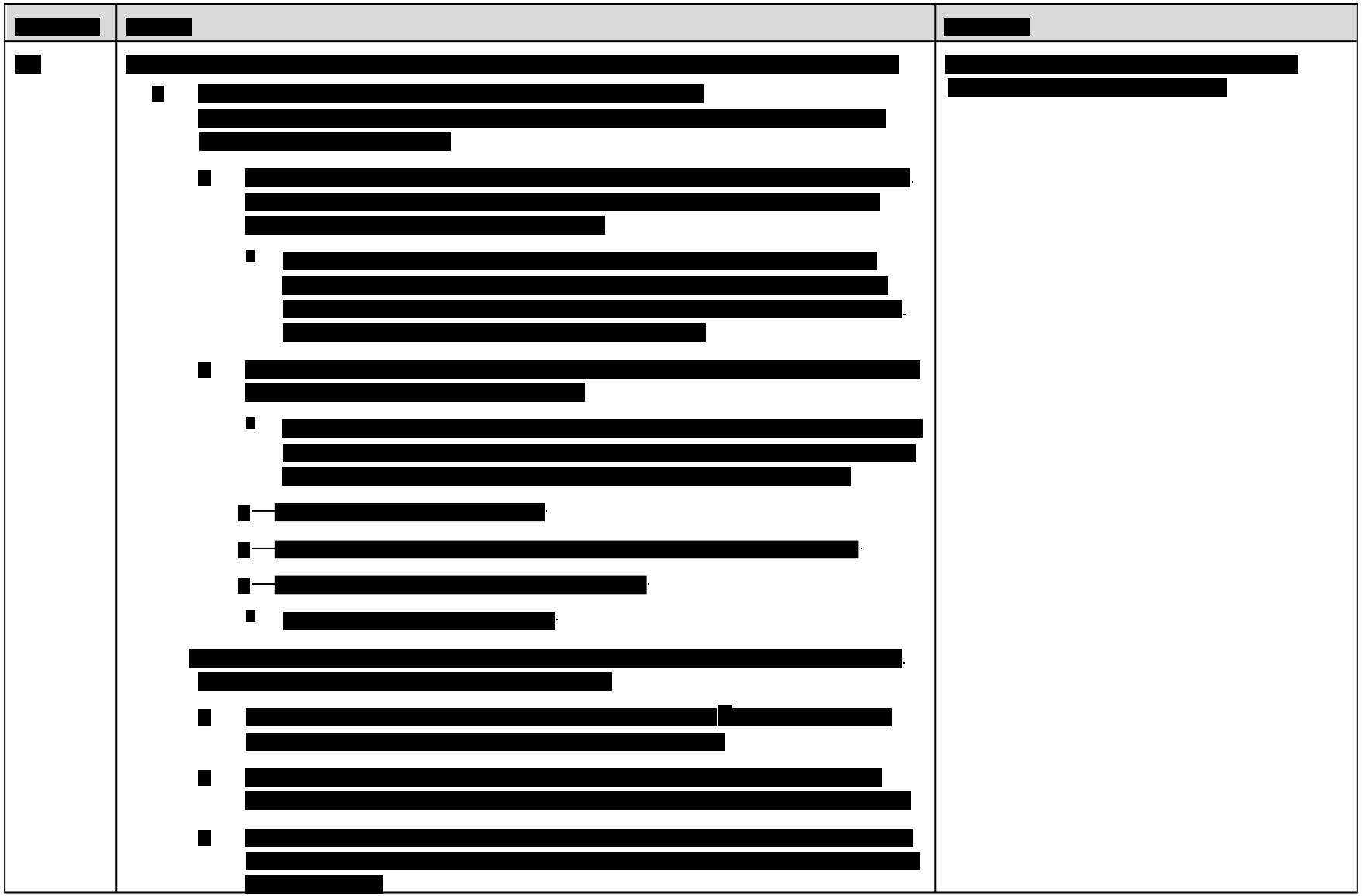

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