Investigational Product	TTI-621 (SIRPα-IgG1 Fc)
Protocol Number	TTI-621-03
IND Number	129118
Phase of Clinical Development	I/II
Protocol Title	A Phase I/II Study of TTI-621 in Combination with Doxorubicin in Patients with Unresectable or Metastatic High-Grade Leiomyosarcoma
Version and Date	Version 2.0, 17 June 2022
Sponsor Contact	PPD MD, PhD PPD Trillium Therapeutics, a Pfizer Company 100 Cambridgepark Drive, Suite 510 Cambridge, MA, 02140 USA

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1. PROTOCOL APPROVAL

Protocol Number	TTI-621-03
Version and Date	Version 2.0, 17 June 2022
Protocol Title	A Phase I/II Study of TTI-621 in Combination with Doxorubicin in a Patients with Unresectable or Metastatic High-Grade Leiomyosarcoma

I have read this protocol and confirm that it accurately describes the planned conduct of the study.

PPD

Date

PPD

Trillium Therapeutics, a Pfizer Company

2. SYNOPSIS

Protocol Number	TTI-621-03
Version and Date	2.0, 17 June 2022
Phase of Clinical Development	Phase I/II
Protocol Title	A Phase I/II Study of TTI-621 in Combination with Doxorubicin in Patients with Unresectable or Metastatic High-Grade Leiomyosarcoma
Investigational Product	TTI-621 (SIRPα-IgG1 Fc)
IND Number	129118
Study Population	Patients aged 18 years or older with unresectable or metastatic leiomyosarcoma who have not received prior treatment with anthracyclines (dose expansion); patients with leiomyosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, dedifferentiated liposarcoma, angiosarcoma or epithelioid sarcoma will be allowed to enroll into the dose escalation portion of the study.
General Investigative Plan	A dose escalation will be undertaken in anthracycline-naïve patients with the high grade soft tissue sarcomas subtypes of leiomyosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, dedifferentiated liposarcoma, angiosarcoma or epithelioid sarcoma to evaluate safety of the planned dosing regimen of doxorubicin at 75 mg/m^2 in combination with TTI-621. The study will then be expanded to evaluate clinical activity and safety of TTI-621 at two dose levels in combination with doxorubicin at 75 mg/m^2 in patients with high-grade leiomyosarcoma.
Investigative Sites	Up to 20 centers in the US
Planned Number of Subjects	Up to approximately 80, including up to approximately 18 in the dose escalation portion of the study and approximately 62 subjects in the expansion portion of the study
Enrollment Period	The enrollment period is anticipated to be approximately 18 months in duration, with the first patient anticipated to be enrolled in July 2021 and completion of enrollment anticipated for December 2022
Background and Rationale	Soft tissue sarcomas are a rare, heterogeneous group of mesenchymal tumors, commonly the result of complex chromosomal abnormalities that play a role in disease progression and metastasis. Doxorubicin has been since the 1970s the standard of care for first-line treatment of patients with metastatic or advanced soft tissue sarcoma; however,

doxorubicin activity is poor, with a response rate of 9 - 27%[1,2] and progression-free survival of 3-5 months,[3-5] with cumulative cardiac toxicity that limits its use.[6] TTI-621 is a recombinant soluble fusion protein designed to block the cell-surface protein CD47, which is found on the surface of many normal cell types and at high levels on many malignant tumor cells. CD47 binds to signal regulatory protein alpha (SIRPα) on the surface of macrophages and inhibits their phagocytic activity. This CD47-mediated inhibition of macrophage phagocytosis activity is an important mechanism through which cancer cells can escape immune-mediated clearance, and high levels of CD47 correlate with poor clinical prognosis across a number of cancer types. TTI-621 combines CCI CCI of human SIRPα (the binding domain for CD47) with the Fc region of human IgG1, generating a decoy receptor for CD47 on the surface of tumor cells that both over-rides the CD47-mediated inhibition of phagocytosis through the SIRPα portion of the protein and provides a pro-phagocytic stimulation through the IgG1 moiety.

In an analysis of 206 sarcomas, the subtypes with the highest median macrophage scores included non-translocation-related sarcomas, such as leiomyosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, angiosarcoma, dedifferentiated liposarcoma and epitheliod sarcoma.[7] In another study of tissue microarrays of 1242 sarcoma specimens conducted to further the understanding of the sarcoma immune landscape, tumor-associated macrophage infiltration and expression of the targetable macrophage-related immune checkpoint CD47/SIRPα was evaluated.[8] This study showed that the M2-like (CD163+) macrophages were the predominant phenotype, which agrees with findings in melanoma,[9] non-small cell lung cancer,[10] and colorectal cancer.[11,12] The presence of large numbers of M2-like macrophages suggests a highly immunosuppressive tumor microenvironment but due to the plasticity of tumor-associated macrophage polarization, this could represent anti-tumor immunity that is suppressed-but-poised for reactivation.[13]

Many solid tumors, including brain, breast, colon, gastric, kidney, soft tissue sarcomas including leiomyosarcoma, osteosarcoma, liver, lung, melanoma, ovarian, pancreatic, and prostate tumors have also been found to express high levels of CD47.[14-18] In many of these cases, high expression of CD47 is associated with poor prognosis, thought to be the result of CD47-mediated inhibition of macrophage phagocytosis and escape of immune-mediated clearance. Interruption of the CD47-SIRPα signaling pathway using monoclonal antibodies to CD47 has shown anti-tumor activity in human cancers both *in vitro* and *in vivo* in animal models of human malignancies and in some early clinical trials.[19]

	In a number of animal models of human tumors, the combination of doxorubicin with CD47-targeted antibodies results in enhanced anti-tumor activity and increased macrophage-mediated cell killing and macrophage-mediated phagocytosis of cancer cell lines *in vitro*,[20-23] suggesting that combining TTI-621 with doxorubicin chemotherapy might be more effective than doxorubicin alone in tumor types that express CD47 and have high numbers of macrophages, such as leiomyosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, angiosarcoma, dedifferentiated liposarcoma and epitheliod sarcoma. It is hypothesized that blockade of CD47-mediated immune evasion and concomitant activation of phagocytosis with TTI-621 will be clinically beneficial in patients with sarcoma subtypes in which CD47 is expressed and macrophage scores are increased. In addition, CCI [redacted] Thus, the primary goals of this clinical trial are to evaluate the safety of TTI-621 administered in combination with standard-of-care doxorubicin in anthracycline-naïve patients with high-grade soft tissue sarcomas and to further evaluate clinical activity and safety in the leiomyosarcoma subpopulation.
Study Design	This is a multi-center, open-label study designed to evaluate TTI-621 administered in combination with doxorubicin. The first portion of the study will evaluate the safety of increasing dose levels of TTI-621 in combination with doxorubicin at the standard dose of at 75 mg/m^2 in patients with high-grade leiomyosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, dedifferentiated liposarcoma, angiosarcoma or epithelioid sarcoma who have not received more than one prior line of therapy for advanced disease and have not received an anthracycline in any setting (neoadjuvant, adjuvant or as treatment for advanced of metastatic disease). Two dose levels of TTI-621 in combination with doxorubicin will be selected for further evaluation in an expansion phase in which patients with leiomyosarcoma who have not received more than one prior line of therapy for advanced disease and have not received an anthracycline in any setting (neoadjuvant, adjuvant or as treatment for advanced of metastatic disease). The diagnosis of leiomyosarcoma will be confirmed at a central laboratory; the patient may be enrolled based on a current or most recent pathology report that provides sufficient detail to support derivation of the histologic interpretation but a pre-treatment tissue specimen must be made available for confirmation during screening or within the first cycle of treatment. In the event that the diagnosis is not confirmed during central review, the patient must be replaced for purposes of meeting the statistical requirements of the study but may be allowed to continue on treatment after discussion with the

Sponsor Medical Monitor. Additional key inclusion criteria are ECOG performance status 0-1 (Appendix A), age ≥18 years, measurable disease by RECIST v1.1, and adequate cardiac and end organ function. Patients with prior exposure to anthracyclines will be excluded.

In the Phase I dose escalation portion of the study, the primary objective is assessment of the safety of escalating dose levels of TTI-621 in combination with doxorubicin at the standard dose of 75 mg/m^2. Up to approximately 18 patients are planned to be enrolled in this portion of the study to evaluate three dose levels of TTI-621: 0.2 mg/kg (Dose Level 1), 0.7 mg/kg (Dose Level 2) and 2.0 mg/kg (Dose Level 3). Enrollment will be open to patients with high-grade leiomyosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, dedifferentiated liposarcoma, angiosarcoma and epithelioid sarcoma. Two dose levels will be selected for evaluation in patients with leiomyosarcoma in the Phase II expansion portion of the study.

The primary objectives of the Phase II expansion portion of the study are evaluation of the safety and investigation of clinical activity of the doxorubicin and TTI-621 combination for up to 18 weeks and TTI-621 monotherapy given on an ongoing basis after completion of the 18-week combination in patients with leiomyosarcoma. Clinical activity will be based on assessment of the overall response rate by RECIST v1.1 in expansion cohorts: doxorubicin at 75 mg/m^2 in combination with TTI-621 at a lower dose (Cohort A) and doxorubicin at 75 mg/m^2 in combination with TTI-621 at a higher dose (Cohort B). Up to approximately 31 patients will be treated in each cohort, for a total of approximately 62 patients in this portion of the study.

Secondary objectives include further evaluation of the safety of the combination and assessment of other indications of clinical benefit, including progression-free survival, overall survival, duration of response, and clinical benefit rate as defined by RECIST v1.1 criteria.

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The study will consist of a 28-day screening period, a treatment period in which patients will receive doxorubicin in combination with TTI-621 in 21-day cycles for a maximum of six cycles, followed by continued treatment with TTI-621 monotherapy in 28-day cycles until documentation of objective disease progression or development of unacceptable toxicity, and a long-term follow-up period to assess overall survival.

In the combination portion of the study, Cycle 1 through Cycle 6, doxorubicin will be administered at 75 mg/m^2 on Day 1 of each 21-day cycle. Doxorubicin should be administered through a free-flowing catheter at 75 mg/m^2 by intravenous infusion in less than 60 minutes. A maximum of six cycles of doxorubicin (18 weeks of treatment) is permitted. Required prophylaxis for emesis and cardioprotection, as well as guidelines for prophylaxis with G-CSF for prevention of febrile neutropenia, is described in Section 5.2.1. In Cycle 1 through Cycle 6, following prophylaxis as described in Section 5.2.1 for possible infusion-related reactions, TTI-621 will be administered by intravenous infusion over 120 minutes on Day 1 and Day 8 of each 21-day cycle. Beginning with Cycle 2, the infusion period may be reduced to 60 minutes at the Investigator's discretion if the patient has not experienced infusion-related reaction.

For the purposes of safety decisions that guide cohort expansion and considerations of TTI-621 dose adjustment in the dose escalation portion of the study, the dose-limiting toxicity safety evaluation period will consist of the 21-day Cycle 1. Subjects will be considered evaluable for dose-limiting toxicity (DLT) if they received doxorubicin on Day 1 of Cycle 1 and TTI-621 on Day 1 and Day 8 of Cycle 1. A patient who withdraws from the study during Cycle 1 in the absence of objective disease progression or DLT will be replaced. If a dose-limiting toxicity as defined in Section 5.4 is encountered in one patient in the initial three patients in a dose cohort, three additional patients will be enrolled in accordance with the standard 3+3 study design. The maximum tolerated dose (MTD) for this study will be defined as the maximum evaluated TTI-621 dose level at which <33% of patients within a dose cohort experience dose-limiting toxicity when administered in combination with doxorubicin at 75 mg/m^2. While three pre-defined TTI-621 dose levels are anticipated, intermediate dose levels may be

	studied to more closely characterize the safety profile of TTI-621 in combination with doxorubicin. After three patients in a dose cohort, or six patients in an expanded dose cohort, complete the 21-day dose-limiting toxicity assessment period, the incidence of dose-limiting toxicity, treatment-related safety observations and other available data, such as pharmacokinetic data, will be reviewed by the Sponsor Medical Monitor, Sponsor and Investigators. If no patient in a three-patient cohort or no more than one patient in a six-patient dose cohort experiences treatment-related dose-limiting toxicity, the dose level will be deemed safe and dose escalation may proceed unless there are other unsuspected but concerning safety observations that suggest either an expansion of the current dose level or implementation of an intermediate dose level. After completion of Cycle 6, doxorubicin will be discontinued as per standard of care to avoid development of cumulative cardiac toxicity. Thereafter, beginning with Cycle 7, TTI-621 will be administered as monotherapy on Day 1 and Day 15 of 28-day cycles until documentation of disease progression or unacceptable toxicity. Objective disease assessments will be performed after every second cycle of treatment for approximately 50 weeks and after every third cycle thereafter. A patient enrolled in an expansion cohort who withdraws or is withdrawn from the study prior to completion of two cycles of treatment and objective disease assessment after the second cycle for a reason other than disease progression or safety will be replaced in order to meet the statistical criteria for the Simon two-stage study design. Patients who withdraw from the study without objective evidence of disease progression will be followed until documentation of disease progression or initiation of another treatment. All patients will be followed in the Long-Term Follow-Up period for survival. The mechanism of immunotherapy is mechanistically distinct from other types of therapy. The patterns of response and progression to immunotherapeutic agents, such as TTI-621, often differ temporally, qualitatively and quantitatively from those observed with cytotoxic and targeted agents. The goal of immunotherapy is to overcome immunosuppression induced by a tumor and its microenvironment, thereby allowing the immune system to develop or activate an immune response that targets and kills cancer cells. Some patients have experienced pseudo-progression, in which tumor burden showed an initial surge followed by shrinkage, usually at around four weeks, that led to development of immune-related disease response criteria that supports continued treatment beyond progression in patients whose clinical conditions have not worsened and who have not experienced severe toxicities. Recognizing that immunotherapy

	represents a paradigm shift in oncology treatment, patients with an early observation of disease progression but without deterioration in clinical conditions or unacceptable toxicity and who consent should continue treatment until disease progression is verified by a repeated disease assessment at least four weeks later.
Guidelines for Cohort Assignment	The dose escalation portion of the study carries a traditional 3+3 design to evaluate three dose levels of TTI-621. Standard guidelines for enrollment for the 3+3 design will be followed, with requirement that three patients complete the 21-day dose-limiting toxicity assessment period (six patients in the case of an expanded dose cohort) before the next dose cohort is open to enrollment. However, recognizing that leiomyosarcoma is a rare disease and expecting that patients with leiomyosarcoma may be eager to participate in the study, careful modifications to the enrollment schema have been developed to avoid having to withhold enrollment for these patients. During the dose escalation portion of the study, eligible patients will be enrolled to the cohort that is open at the time they present to the study. Based on known safety of the lowest planned dose of TTI-621, 0.2 mg/kg, gleaned from other clinical trials, it is anticipated that this dose will serve as the TTI-621 dose level for Cohort A. Thus, expansion Cohort A will open to enrollment once that dose level is judged to be safe in the dose escalation portion of the study and the next dose cohort is open to enrollment. If a dose escalation cohort and expansion Cohort A are open to enrollment at the same time, priority for enrollment will be given to the dose escalation cohort and enrollment into expansion Cohort A will be strictly limited to those patients who present to the study after enrollment to a dose escalation cohort is closed and meet all the eligibility criteria for the expansion portion of the study (including documentation of the leiomyosarcoma indication). When both expansion cohorts are open to enrollment, assignment of eligible patients will be made on an alternating basis, with cohort assignment made by the contract research organization overseeing the study on behalf of the sponsor independent of investigator input and based strictly on chronology of verification of eligibility of patients as they complete screening assessments.
Duration of Treatment and Subject Participation	Subjects may receive TTI-621 in combination with doxorubicin for a maximum of six cycles (18 weeks), with six cycles providing the maximum cumulative exposure of doxorubicin. It is intended that each patient will receive six cycles of doxorubicin as fewer than six cycles provides less benefit to the patient compared to six or more cycles[24] and guidelines for prophylaxis for prevention of doxorubicin-mediated dose-limiting neutropenia are provided in Section 5.2.1. Patients may continue on study and receive TTI-621 monotherapy thereafter until disease progression. With a 28-day screening period and an estimated 11 months

	of treatment, it is anticipated that patients may participate in the active portion of the study for up to approximately one year.
Inclusion Criteria	**General** 1. Written informed consent obtained prior to performing any study-specific procedure, including screening procedures 2. Men and women ≥ 18 years of age 3. ECOG Performance Status 0 or 1 4. Patients enrolled onto the dose expansion cohorts must agree to pre-treatment and on-treatment biopsies if deemed safe and feasible by the treating physician **Disease Characteristics** 5. Histologically-confirmed high-grade soft tissue sarcoma that is metastatic or locally advanced and not amenable to curative treatment with surgery or radiation • In the dose escalation portion of the study, indications will be limited to high-grade leiomyosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, dedifferentiated liposarcoma, angiosarcoma and epithelioid sarcoma • In the expansion portion of the study, enrollment will be restricted to high-grade leiomyosarcoma that is histologically-confirmed at a central laboratory. The patient may be enrolled based on a current or most recent pathology report that provides sufficient detail to support derivation of the histologic interpretation but a pre-treatment tissue specimen must be made available for confirmation during screening or within the first cycle of treatment 6. Objective evidence of disease progression unless disease is newly-diagnosed 7. Measurable disease per RECIST v1.1 (expansion cohorts); target lesions must not be chosen from a previously-irradiated field unless there has been radiographically and/or pathologically documented tumor progression in that lesion prior to enrollment. **Organ Function** Adequate organ and hematologic function as defined below: 8. Serum AST and ALT ≤ 3 x upper limit of normal (ULN); ≤ 5 x ULN in the presence of liver metastasis 9. Serum bilirubin (total) ≤ 1.5 x ULN (≤ 2 x ULN if hyperbilirubinemia is due to Gilbert's syndrome) 10. Serum creatinine ≤1.5 x ULN OR creatinine clearance/estimated glomerular filtration rate (eGFR) ≥40 mL/min/1.73 m^2 if serum creatinine is >1.5 x ULN

	11. Hemoglobin ≥9 g/dL; packed red blood cell transfusions are not allowed in the week preceding screening evaluation 12. ANC ≥ 1.5 × 10^9/L 13. Platelet count ≥ 100 × 10^9/L 14. INR ≤ 1.5 x ULN (≤ 2.5 x ULN if on anti-coagulants) and PTT ≤ 5 seconds above the ULN unless receiving anti-coagulation therapy; patients on full-dose anti-coagulation must be on a stable dose of oral anti-coagulant or low molecular weight heparin, have therapeutic INR, no active bleeding (defined as within 14 days prior to first dose of study medication) and no pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices) 15. Left ventricular ejection fraction (LVEF) determined by echocardiogram or multigated acquisition scan >50%
	Previous Therapy 16. No more than one prior treatment regimen for advanced disease, which is limited to gemcitabine with docetaxel 17. Anthracycline-naïve: anthracycline in the neoadjuvant/adjuvant setting renders the patient ineligible for participation 18. Patients who were treated with a prior chemotherapy regimen must have been completed treatment at least three weeks before initiation of study treatment 19. All adverse events from prior treatment must be NCI CTCAE v5 Grade ≤ 1, except alopecia and stable neuropathy, which must have resolved to Grade ≤ 2 or baseline 20. Radiotherapy, including palliative radiotherapy, completed at least two weeks prior to treatment; palliative radiation to non-target lesions while on study is allowed **Contraception** 21. Refer to Appendix D for reproductive criteria for male and female participants. Female patients of childbearing potential must have a negative serum beta human chorionic gonadotropoin pregnancy test result at screening and at baseline before the first study drug administration.
Exclusion Criteria	**General** 1. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members. **Cardiovascular System**

	2. History of acute coronary syndromes, including myocardial infarction, coronary artery bypass graft, unstable angina, coronary angioplasty or stenting within 24 weeks prior to first administration of study drug 3. History of or current Class II, III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system or symptomatic or poorly controlled cardiac arrhythmia 4. Uncontrolled or poorly-controlled hypertension (defined as systolic blood pressure >160 mm Hg) for more than four weeks despite optimal medical management **General and Infectious Disease** 5. Child-Pugh Class C 6. Any comorbidity or concomitant medication or other condition that in the opinion of the Investigator and/or Sponsor Medical Monitor renders the patient unsuitable for participation in the trial or unlikely to fully comply with study procedures, restrictions and/or requirements that are considered relevant for evaluation of the efficacy or safety of the trial drug Consideration should be given to lack of currently-available immunoprotection against SARS-CoV-2 as a condition that may render a patient unsuitable for participation in the trial or unlikely or unable to fully comply with study procedures, restrictions and/or requirements that are considered relevant for the evaluation of the efficacy or safety of study treatment 7. Uncontrolled intercurrent illness, including active or chronic infection requiring systemic therapy or oral or systemic antibiotics within 14 days prior to study start 8. History of non-viral hepatitis or cirrhosis, alcohol abuse or active tuberculosis 9. Administration of live attenuated vaccines within 28 days prior to start of treatment or anticipated need for vaccination with live attenuated vaccine during the study 10. Major surgery within 28 days of scheduled Cycle 1 Day 1 dosing or minor surgery within seven days prior to initiation of study treatment or elective or planned major surgery to be performed during the course of the clinical trial **CNS Disease Considerations** 11. History or evidence of known CNS metastases or carcinomatous meningitis; patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least seven days prior to study

	treatment; this exception does not include carcinomatous meningitis which is excluded regardless of clinical stability **Coagulation Considerations** 12. Chronic therapy with nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., indomethacin, ibuprofen, naproxen or similar agents) or other anti-platelet agents (e.g., clopidogrel, ticlopidine, dipyridamole, anagrelide); aspirin up to 325 mg per day is permitted 13. Significant bleeding disorders, vasculitis or a significant bleeding episode from the GI tract within three months prior to study entry **Immune System** 14. History of severe hypersensitivity reactions to antibodies 15. Systemic steroid therapy (> 10 mg daily prednisone or equivalent) or any other form of immunosuppressive therapy within seven days prior to the first dose of study treatment; topical, inhaled, nasal and ophthalmic steroids are not prohibited 16. History of autoimmune disease that has required systemic treatment with disease-modifying agents, corticosteroids, or immunosuppressive drugs unless in the opinion of the investigator the patient is in a complete and durable remission; physiologic replacement therapies, such as thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, is allowed 17. Prior organ transplantation including allogeneic or autologous stem cell transplantation **Oncology** 18. Concurrent or previous other malignancy within two years of study entry with the exception of cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intra-epithelial neoplasm, carcinoma *in situ* of the cervix, or other non-invasive or indolent malignancy 19. Concurrent enrollment in another therapeutic clinical study 20. Prior treatment with anti-CD47 or anti-SIRPα therapy 21. Prior radiation to mediastinal/pericardial region
Objectives	**Primary Objectives** • Evaluate the safety of escalating dose levels of TTI-621 when administered in combination with 75 mg/m^2 doxorubicin in 21-day cycles and establish the maximum tolerated dose level of TTI-621 when administered in combination with doxorubicin • Evaluate the safety of selected dose levels of TTI-621 when administered in combination with 75 mg/m^2 doxorubicin in 21-day cycles and then as monotherapy in 28-day cycles until documentation of objective disease

	progression • Investigate clinical activity assessed as overall response rate of TTI-621 administered in combination with 75 mg/m^2 doxorubicin for up to six cycles (18 weeks) and then as monotherapy until documentation of objective disease progression **Secondary Objectives** • Further assess safety of the selected dose levels of TTI-621 administered in combination with 75 mg/m^2 doxorubicin • Describe other evidence of clinical benefit CCI [redacted]
Endpoints	**Primary** • Overall safety profile as assessed by the type, frequency, severity, timing and causal relationship of any adverse events, changes in vital signs, ECG, serum chemistry or other laboratory assessment, treatment delays or discontinuations for patients enrolled into the dose escalation portion of the study • The percentage of patients with objective response (CR + PR) as defined by RECIST v1.1 criteria **Secondary** • Overall safety profile as assessed by the type, frequency, severity, timing and causal relationship of any adverse events, changes in vital signs, ECG, serum chemistry or other laboratory assessment, treatment delays or discontinuations for patients enrolled into the selected dose level cohorts in the expansion portion of the study • Progression-free survival (PFS), overall survival (OS), disease control rate (DCR [CR + PR + SD]), duration of response (DOR), duration of disease control, time to progression and time to new metastases as defined by RECIST v1.1 criteria, time to worsening of ECOG performance status, time to worsening of patient-reporting outcomes assessments

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Drug Product TTI-621	TTI-621 (SIRPα-IgG1 Fc) CCI combining the sequences CCI human SIRPα (the binding domain for CD47) with the Fc region of human IgG1. TTI-621 Drug Product is formulated as CCI

	CCI [redacted], TTI-621 Drug Product is CCI [redacted] administered by intravenous infusion over 120 minutes. The dose of TTI-621 will be based upon the dose level cohort to which the patient is assigned. Prophylaxis with acetaminophen, anti-histamine and steroid will be given prior to initiation of TTI-621 infusion to eliminate or reduce the occurrence or grade of immune-related reaction. In the absence of infusion-related reaction, the duration of infusion may be reduced to 60 minutes beginning with Cycle 2. On days when TTI-621 and doxorubicin are both administered, doxorubicin will be administered prior to infusion of TTI-621. On each day of TTI-621 administration, a 60-minute observation period will follow TTI-621 infusion and vital signs will be assessed at 30-minute intervals during this observation period; at the Investigator's discretion, the duration of the observation period may be decreased after completion of Cycle 1 for a patient who has not experienced infusion-related reaction.
Reference Product Doxorubicin	Doxorubicin is considered standard of care in the intended patient population and will be used in accordance with standard of care with intravenous infusion at a dose of 75 mg/m^2 on Day 1 of each 21-day cycle for a maximum of six cycles (18 weeks). Doxorubicin should be made up to a volume of 100 mL and administered through a free-flowing catheter at 75 mg/m^2 by intravenous infusion in less than 60 minutes. The rate of infusion should be decreased if erythematous streaking along the vein proximal to the site of infusion or facial flushing occur. Doxorubicin is emetogenic and prophylaxis for emesis prior to each infusion of doxorubicin should be given. Institutional guidelines for effective prophylaxis, including specific agents, additional agents and regimens, are acceptable. Cardioprotective prophylaxis must be implemented no later than with initiation of Cycle 5. ASCO guidelines for use of WBC growth factors[25] provide that 'prophylactic use of WBC growth factors for prevention of febrile neutropenia is warranted when the risk of febrile neutropenia is approximately 20% or higher and no other equally effective and safe regimen that does not require CSFs is available. Primary prophylaxis is recommended for the prevention of febrile neutropenia in patients who are at high risk on the basis of age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. The NCCN guidelines for hematopoietic growth factors[26] classify soft tissue sarcoma treated with doxorubicin as an example of disease setting and chemotherapy regimen with a

	high risk for febrile neutropenia (>20%) and recommends G-CSF prophylaxis for patients with high risk (>20%) of febrile neutropenia. Thus, all patients receiving TTI-621 in combination with doxorubicin should receive prophylaxis with G-CSFs for prevention of febrile neutropenia. Suggested prophylaxis is pegfilgrastim and discussion with the Sponsor Medical Monitor is encouraged. The Single Reference Safety Document (SRSD) for doxorubicin is the US Product Insert (USPI).
Statistical Considerations	Based on a standard 3+3 design, up to approximately six patients may be enrolled in each dose level cohort evaluated during the dose escalation portion of the study; a minimum of nine and a maximum of 18 patients who complete the safety review period is anticipated. The sample size for the dose level expansion cohorts is selected to obtain a reasonable estimate of clinical benefit, defined for this study as response rate defined by RECIST v1.1 criteria, to be used for planning future studies. A Simon two-stage design will be used for each dose cohort; in the Simon two-stage design and assuming a baseline overall response rate of 10% with doxorubicin monotherapy and an alternative of 25%, a power of 90% and one-sided Type 1 error set at 0.20, each dose level cohort will require 18 patients enrolled and evaluable for response in Stage 1. With at least two clinical responses, an additional 13 patients will be enrolled in Stage 2. The combination will be considered worthy of further study if at least five clinical responses observed in either 31-patient cohort.
Dose Delays, Dose Modifications, Guidelines for Treatment Discontinuation and Study Withdrawal	Patients who enter the study with symptoms or laboratory values equivalent to NCI CTCAE Grade 1 or Grade 2 should not have dose reductions related to the persistence or mild worsening of those symptoms or laboratory values. Dose reductions may be warranted if worsening of symptoms or laboratory values is clinically significant in the opinion of the Investigator and in the case of unacceptable treatment-related adverse events. Recognizing that it may be difficult to make attribution to one agent or the other in the combination regimen and in collaboration with the Sponsor Medical Monitor, best efforts should be made to consider the underlying reason for the worsening of symptoms or development of a treatment-related adverse event so that dosing of the appropriate study drug can be modified. Except in the case of proteinuria, asymptomatic laboratory abnormalities should not result in dose interruptions, modifications, or discontinuation of study therapy unless determined by the Investigator to be clinically significant or life-threatening.

	The Investigator should withdraw a patient from all study-related treatment for any of the following reasons: • An unacceptable adverse event or safety observation, such as a persistent moderate toxicity that is intolerable to the patient, that is in the opinion of the Investigator clearly attributed to TTI-621 • An unacceptable adverse event or safety observation, such as a persistent moderate toxicity that is intolerable to the patient, that is in the opinion of the Investigator clearly attributed to doxorubicin and the patient has received fewer than four cycles of doxorubicin. A patient who has completed four cycles of doxorubicin treatment and experiences an adverse event that requires discontinuation of doxorubicin treatment despite optimal prophylaxis and supportive care and is receiving clinical benefit may be eligible to continue to TTI-621 monotherapy with the next cycle (Cycle 5 or Cycle 6) after discussion with the Sponsor Medical Monitor and provided the patient has not experienced disease progression and TTI-621 re-treatment guidelines as described in Section 9.2.2 are met; the patient may be replaced or an additional patient may be enrolled for the purposes of having a heterogeneous population for evaluation of safety and clinical activity as described in Section 6.7. • Any event which would cause TTI-621 or doxorubicin to be modified by more than two dose reductions or to be held for more than 42 days from the last administered dose and is not attributable to a particular agent of the combination regimen; exception is made for patients who are receiving meaningful clinical benefit and the investigator feels, with Sponsor Medical Monitor concurrence, that continued treatment is in the best interest of the patient • Any treatment-related adverse event that is deemed life-threatening, regardless of grade; exception is made for patients in whom the life-threatening adverse event is attributed to doxorubicin and has occurred despite optimal prophylaxis and medical support and the patient is receiving clinical benefit and has received at least four cycles of doxorubicin treatment and the investigator feels, with Sponsor Medical Monitor concurrence, that continuation with TTI-621 monotherapy would be reasonable; the patient may be replaced or an additional patient enrolled for the purposes of having a heterogeneous population for evaluation of safety and clinical activity as described in Section 6.7. • Documentation of objective (radiographic) disease progression; for patients with asymptomatic progression and in the absence of unacceptable toxicity, the patient should continue treatment and a confirmation scan should be

	conducted at least four weeks later to document objective progression prior to removing patient from study treatment • Unacceptable toxicity which in the opinion of the Investigator cannot be attributed to a specific study agent • An intercurrent illness or change in the patient's condition that renders the patient unsuitable for further treatment in the opinion of the Investigator; exception may be made for patients in whom the intercurrent illness or change in condition is thought to render the patient ineligible for continued treatment with doxorubicin and the patient has received at least four cycles of doxorubicin and is receiving clinical benefit and the investigator feels, with Sponsor Medical Monitor concurrence, that continuation with TTI-621 monotherapy would be reasonable and the patient meets criteria for TTI-621 re-treatment; the patient may be replaced or an additional patient may be enrolled for the purposes of having a heterogeneous population for evaluation of safety and clinical activity as described in Section 6.7. • Significant noncompliance with study protocol • Withdrawal of consent (patient may participate in Long-Term Follow-Up assessment of survival and disease status [if withdrawn prior to documentation of objective disease progression] if consent for this portion of the study is not withdrawn) • Termination of the study by the sponsor

STUDY SCHEMA SUMMARY

In the dose escalation portion of the study, eligible patients with high-grade leiomyosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, dedifferentiated liposarcoma, angiosarcoma or epithelioid sarcoma will receive doxorubicin at 75 mg/m^2 and escalating doses of TTI-621 in a standard 3+3 design. For the expansion portion of the study, a low dose (Cohort A) and a high dose (Cohort B) of TTI-621 will be selected for evaluation with 75 mg/m^2 doxorubicin in patients with high-grade leiomyosarcoma using a Simon two-stage design. Due to cumulative toxicity that limits its use, doxorubicin is administered on Day 1 of 21-day cycles for a maximum of six cycles (18 weeks). In Cycle 1 through Cycle 6, TTI-621 will be administered on Day 1 and Day 8 of each 21-day cycle. Beginning with Cycle 7, TTI-621 will be administered as monotherapy on Days 1 and 15 of 28-day cycles.

During the dose escalation portion of the study, eligible patients will be enrolled to the cohort that is open at the time they present to the study. Based on known safety of the lowest planned dose of TTI-621, 0.2 mg/kg, gleaned from other clinical trials, it is anticipated that this dose will serve as the TTI-621 dose level for Cohort A. Thus, expansion Cohort A will open to enrollment once that dose level is judged to be safe in the dose escalation portion of the study. If a dose escalation cohort and expansion Cohort A are open to enrollment at the same time, priority for enrollment will be given to the dose escalation cohort and enrollment into expansion Cohort A will be limited to those patients who present to the study after enrollment to a dose escalation cohort is closed and meet all the eligibility criteria for the expansion portion of the study (including documentation of the leiomyosarcoma indication).

When both expansion cohorts are open to enrollment, cohort assignment will be made on an alternating basis, with assignment made by the CRO overseeing the study on behalf of the sponsor independent of investigator input and based strictly on chronology of verification of eligibility of patients as they complete screening assessments.

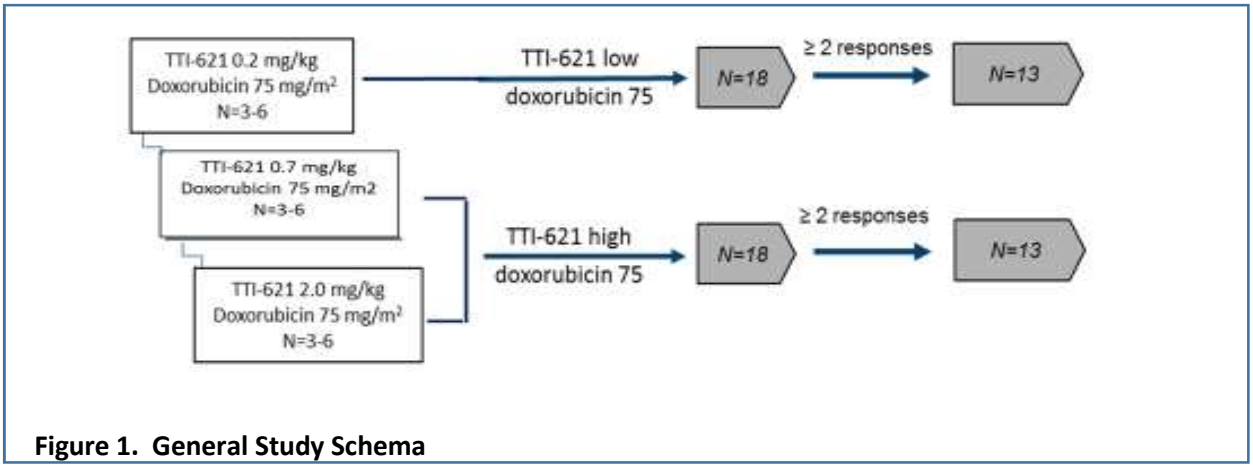

Figure 1. General Study Schema

In the Simon two-stage design and assuming a baseline ORR of 10% with doxorubicin monotherapy and an alternative of 25%, a power of 90% and one-sided Type 1 error set at 0.20, each dose level cohort will require 18 patients enrolled and evaluable for response in Stage 1; with at least 2 clinical responses, an additional 13 patients will be enrolled in Stage 2. The combination will be considered worthy of further study if at least five clinical responses are observed in either 31-patient cohort.

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ABBREVIATIONS

ABCL	aggressive B-cell lymphoma
CCI	[redacted]
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BUN	blood urea nitrogen
CLL	chronic lymphocytic leukemia
C_{max}	maximum blood concentration
CNS	central nervous system
CR	complete response
CRO	contract research organizaiton
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	cutaneous T-cell lymphoma
D	Day
DCR	disease control rate
DILI	Drug Induced Liver Injury
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EC_{50}	effective half-maximal concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDC	electronic data capture
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
CCI	[redacted]
EOI	End of Infusion
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
FFPE	fresh-fixed paraffin embedded
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
HCl	Hydrochloride
HIPAA	Health Information Portability and Accountability Act
HL	Hodgkin lymphoma

IBCL	indolent B-cell lymphoma
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
CCI	[redacted]
IV	intravenous(ly)
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MF	mycosis fungoides
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NA	not available
NBF	neutral-buffered formalin
NCI	National Cancer Institute
NE	not evaluable
NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
NSAID	nonsteroidal anti-inflammatory drug
ORR	overall response rate
OS	overall survival
P-gp	P-glycoprotein
PD	pharmacodynamics; progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand-1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PS	performance status
PSSA	Pfizer SAE Submission Assistant
PTCL	peripheral T-cell lymphoma
QLQ-C30	Quality-of-Life Questionnaire Core 30
QoL	quality of life
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAP	Statistical Analysis Plan
SD	stable disease
SIRPα	signal regulatory protein alpha

SMPC	Summary of Product Characteristics
SRSD	Single Reference Safety Document
SUSAR	suspected unexpected serious adverse reactions
$t_{½}$	terminal half-life
TAM	tumor-associated macrophage
TCL	T-cell lymphoma
CCI	[redacted]
THC/CBD	tetrahydrocannabinol/cannabidiol
TEAE	treatment-emergent adverse event
T_{max}	time to C_{max}
T-Vec	talimogene laherparepvec
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
USPI	United States Product Insert
WBC	white blood cell
WOCBP	woman of child-bearing potential

3. INTRODUCTION

3.1. CD47 and Signal Regulatory Protein Alpha (SIRPα)

CD47 is a transmembrane glycoprotein normally expressed on all hematopoietic cells and additionally on epithelial and mesenchymal cells in many tissues.[27,28] CD47 binds several integrin proteins and the extracellular matrix protein thrombospondin-1 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.[29-34]

Hematologic malignancies have been shown to have high expression of CD47, including non-Hodgkin lymphoma (NHL), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), multiple myeloma, acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS).[35-41] Solid tumors have also been found to display high CD47 expression, including brain, breast, colon, gastric, kidney, soft tissue sarcomas including leiomyosarcoma, osteosarcoma liver, lung, melanoma, ovarian, pancreatic, and prostate tumors.[14-18] In many of these cases, high expression of CD47 is associated with poor prognosis.

CD47 binds to signal regulatory protein alpha (SIRPα), a transmembrane glycoprotein receptor consisting of 3 extracellular immunoglobulin-like domains and a cytoplasmic tail that triggers phosphatase-mediated signaling. Signal regulatory protein alpha (SIRPα) is found on macrophages, monocytes, granulocytes, dendritic cells, and neurons.[42] The interaction of CD47 with SIRPα on the surface of macrophages leads to inhibition of macrophage-mediated phagocytosis.[43] The association between high levels of CD47 and poor clinical prognosis in patients is postulated to be due to the inhibitory CD47 signal, which serves as an important mechanism by which malignant cells escape immune-mediated clearance. Interruption of the CD47-SIRPα signaling pathway using monoclonal antibodies to CD47 has shown anti-tumor activity in human cancers both *in vitro* and *in vivo* in animal models of human malignancies and in some early clinical trials.

3.2. Regulation of Macrophage Phagocytic Activity

Macrophage-mediated phagocytosis is regulated by both activating (“eat”) and inhibitory (“do not eat”) signals. Of the latter, the best characterized inhibitory signal is CD47, which suppresses phagocytosis by binding SIRPα on the surface of macrophages.[43] Upon binding to CD47, immunoreceptor tyrosine-based inhibitor motifs in the cytoplasmic tail of SIRPα become phosphorylated, resulting in recruitment and activation of downstream phosphatases, including SHP-1 and SHP-2, ultimately leading to inhibition of phagocytosis. The inhibition is thought to be mediated through deactivation of the contractile cytoskeletal activity involved in pulling the target cell into a macrophage for ingestion.[44] Interestingly, this strategy of immune evasion is used by both differentiated cancer cells and cancer stem cells.[45]

As noted above, elevated expression of CD47 has been correlated with poor clinical outcome. For example, overall survival was significantly lower for diffuse large B-cell lymphoma (DLBCL) or mantle cell lymphoma patients who had elevated CD47 expression.[36] CD47 expression was independently prognostic of DLBCL disease progression per multivariate analyses incorporating key prognostic factors. Similarly, patients with CLL that expressed high levels of CD47 experienced a significantly worse event-free survival compared with those whose tumor expressed lower expression levels.[36] Similar trends have been reported in other hematologic malignancies[35,37,39] and in solid tumors.[16,18,46,47] Indeed, evidence exists that

increased CD47 expression may be involved in the transition from low-risk to high-risk MDS and possible transformation to AML.[43] These findings are consistent with tumor cells exploiting the suppressive CD47-SIRPα axis to evade macrophage-mediated destruction. Blocking CD47 has emerged as a therapeutic strategy and several anti-CD47 developmental programs are underway to explore this approach.

3.3. TTI-621

Trillium Therapeutics, a Pfizer Company is developing TTI-621 (SIRPα-IgG1 Fc), a recombinant soluble fusion protein created by combining sequences CCI [redacted] of human SIRPα (the CD47 binding domain) with the Fc region of human IgG1 (Figure 2). CCI [redacted]
CCI [redacted]

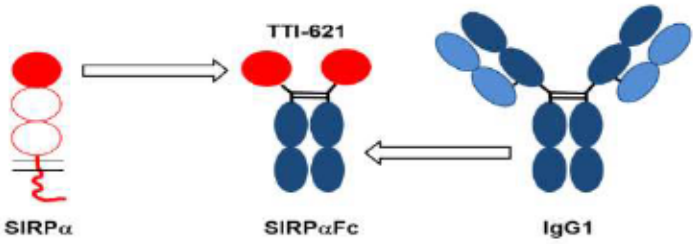


Figure 2. Diagrammatic Structure of TTI-621
TTI-621 consists of the N-terminal domain of human SIRPα (red) linked to a human IgG1 Fc region (blue).

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 proposed mechanism of action for TTI-621 is illustrated in Figure 3. Tumor cells express high levels of the CD47 "do not eat" signal, which suppresses phagocytosis by engaging SIRPα on the surface of macrophages, over-riding 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.

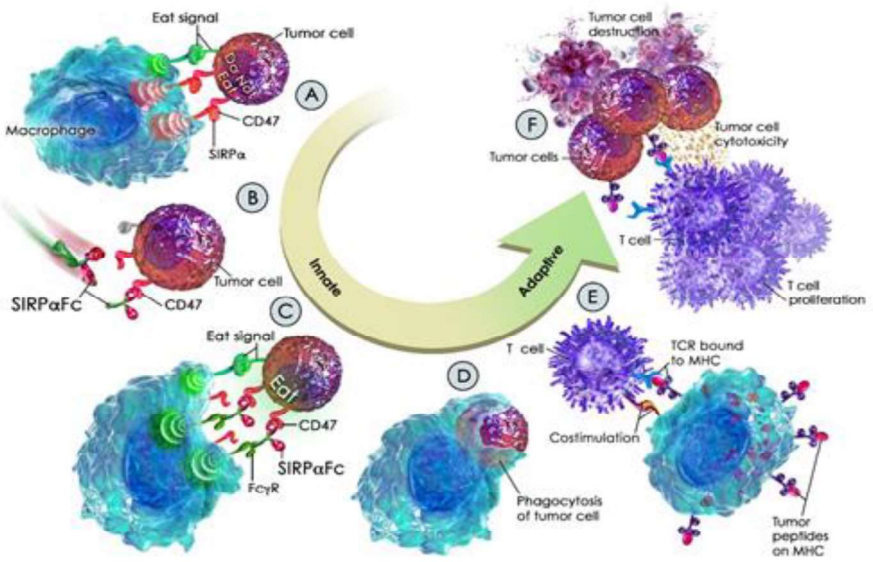


Figure 3. Mechanism of Action of CD47

CD47 on the tumor cell provides a suppressive, anti-phagocytic signal to macrophages through SIRPα (Step A). TTI-621 (SIRPα-IgG1 Fc) binds CD47 on tumor cells (Step B) and engages Fc gamma receptors on macrophages (Step C) resulting in tumor cell phagocytosis (Step D). Following phagocytosis, tumor cell antigens are processed and presented by macrophages as MHC-peptide complexes to T cells (Step E), resulting in T cell activation and tumor cell destruction (Step F).

3.4. Rationale for Patient Population and Study Design

Soft tissue sarcomas are a rare, heterogeneous group of mesenchymal tumors, commonly the result of complex chromosomal abnormalities that play a role in disease progression and metastasis. Surgery with radiotherapy is the most common treatment for localized disease, with 5-year survival rates on the order of only 55% depending on the stage of disease.[48] For patients diagnosed with advanced disease, survival is remarkably poor – on the order of only one to two years.[46-48] Doxorubicin is the standard of care for first-line treatment of patients with metastatic or advanced soft tissue sarcoma; however, doxorubicin activity is poor, with a response rate of 9 - 27%[1,2] and progression-free survival (PFS) of 3-5 months,[3-5] with cumulative cardiac toxicity that limits its use.[6] The cytotoxic chemotherapy regimen of gemcitabine with docetaxel is an alternative to doxorubicin, but does not lead to better results for patients.[52]

Several large Phase 3 studies conducted over the past decade have failed to identify a superior treatment and doxorubicin continues to be the mainstay of treatment for the general population of patients with soft tissue sarcoma despite poor survival and the potential for irreversible cardiotoxicity associated with its use. Thus, there is a clear need for a more effective treatment option for patients with soft tissue sarcoma, leiomyosarcoma being one of the most common subtypes.

Soft tissue sarcoma lesions are often heavily infiltrated by tumor-associated macrophages (TAMs), which can outnumber tumor infiltrating lymphocytes by 10-fold.[7,8,15] Studies have shown higher CD47 expression in soft tissue sarcoma compared to benign tissue.[15] Further, blockade of the CD47-SIRPa axis in preclinical models of leiomyosarcoma can decrease tumor growth and metastasis.[15] Thus, blockade of

high CD47-expressing soft tissue sarcoma tumor cells by TTI-621 may enable phagocytosis of malignant cells by the infiltrating TAMs, potentially resulting in tumor cell destruction and better patient outcomes.

The combination of doxorubicin and CD47-blockade has been shown to enhance anti-tumor activity in multiple solid tumor models, including ovarian, breast and hepatocellular carcinoma.[20-22] In an invasive breast cancer model, anti-CD47 antibody therapy enhanced the effect of doxorubicin by reducing tumor growth and metastatic spread to the lungs.[21] This anti-tumor effect was associated with increased macrophage-mediated killing of breast cancer cells. Moreover, CD47 blockade was found to protect against doxorubicin-induced cytotoxicity by enhancing cardiac tissue viability and function in mice. This cytoprotective effect was attributed to an increase in autophagic flux. In another study, CD47 blockade enhanced macrophage-mediated phagocytosis of hepatocellular carcinoma cell lines in the presence of doxorubicin *in vitro*.[22]

Together, these studies suggest that combining TTI-621 with doxorubicin chemotherapy may be more effective than doxorubicin alone in tumor types that have high CD47 expression and have high numbers of macrophages, such as leiomyosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, angiosarcoma and dedifferentiated liposarcoma.

In an ongoing clinical trial of TTI-621 in patients with relapsed or refractory hematologic malignancies and selected solid tumors (NCT02663518), as of 01 October 2020, 235 patients have been enrolled to evaluate escalating dose levels of TTI-621 and in combination with other treatment regimens. In this study, TTI-621 is administered weekly and doses ranging from 0.05 mg/kg to 2.0 mg/kg have been evaluated. The safety profile is very similar across dose levels, with the primary Grade ≥ 3 treatment-related adverse event being acute but reversible thrombocytopenia which occurred in 22% of patients treated at dose levels of 0.05 mg/kg up to 0.5 mg/kg alone and in combinations and in 24% of patients treated at dose levels ranging from 0.5 mg/kg up to 2.0 mg/kg. Among patients with T cell lymphomas treated with TTI-621 at a dose of 0.2 mg/kg, an overall response rate of 21% has been observed in the intent-to-treat patient. At higher dose levels, up to 2.0 mg/kg, experience is more limited as this portion of the study is still ongoing. As of 12 April 2021, a 19% response rate has been observed in the intent-to-treat population of patients with cutaneous T cell lymphoma at dose levels between 0.7 mg/kg and 2.0 mg/kg; five patients continue to receive treatment with TTI-621 at 2.0 mg/kg and this portion of the study remains open to enrollment.

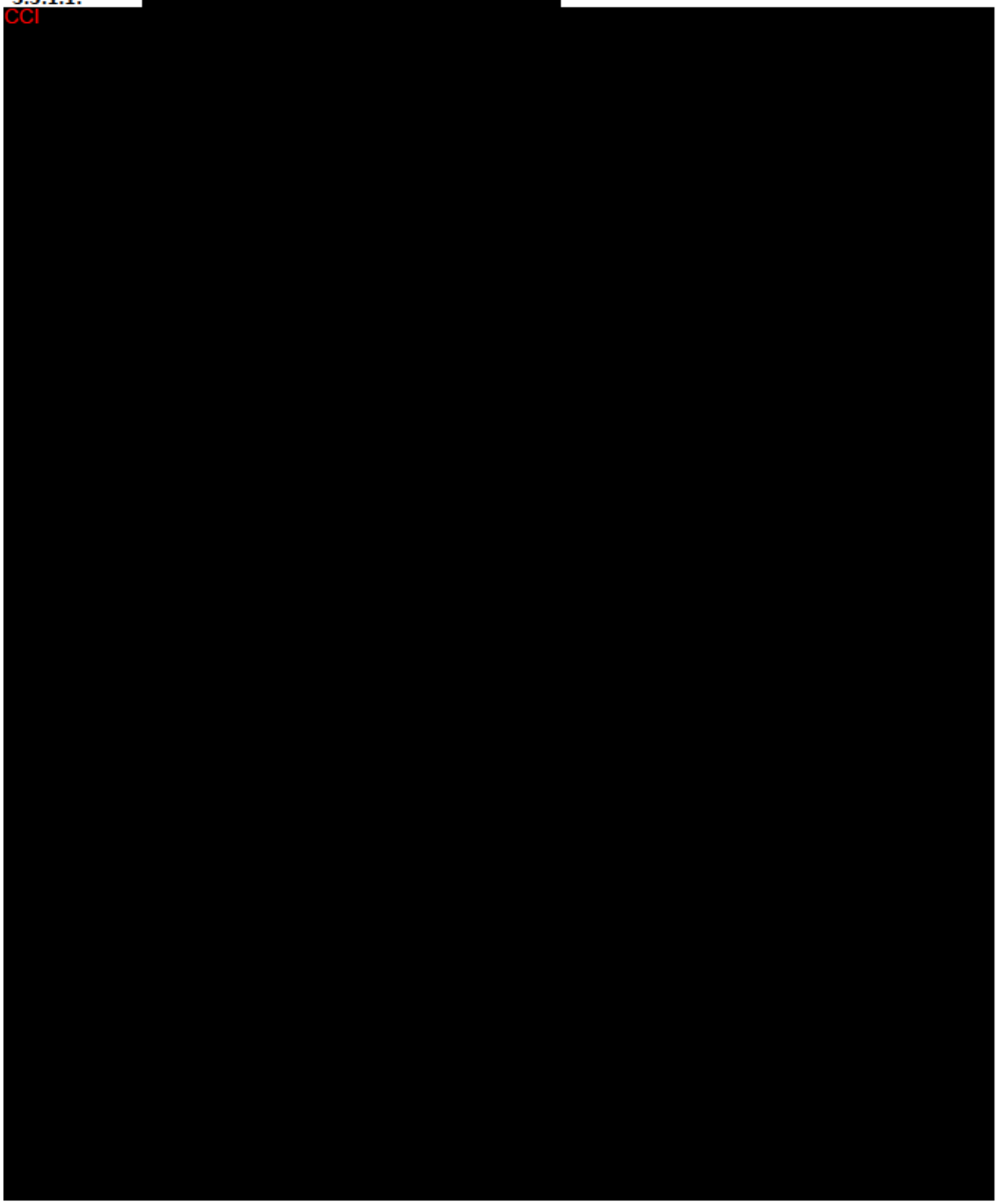
Thus, given the powerful rationale that supports CD47-targeted immune-based therapy in sarcoma, this study will now evaluate TTI-621 in patients with advanced high-grade leiomyosarcoma, one of the most common soft tissue sarcoma subtypes. As a first step, the safety and activity of escalating doses of TTI-21 in combination with doxorubicin administered under the medically-recognized standard dosing regimen (75 mg/m^2 on Day 1 of 21-day cycles for up to six cycles) will be evaluated in the first part of this study, with expansion cohorts to evaluate the safety and activity of a high dose and a low dose of TTI-621 in combination with doxorubicin with the goal of identifying the optimal combination for subsequent clinical evaluations.

3.5. Investigational Medicinal Product TTI-621

3.5.1. Nonclinical Experience with TTI-621

3.5.1.1. CCI

CCI



CCI

[redacted]

Additional information is found in the Investigator's Brochure.

3.5.1.2. CCI

CCI

[redacted]

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

3.5.1.3. **Nonclinical Toxicology of TTI-621**

CCI

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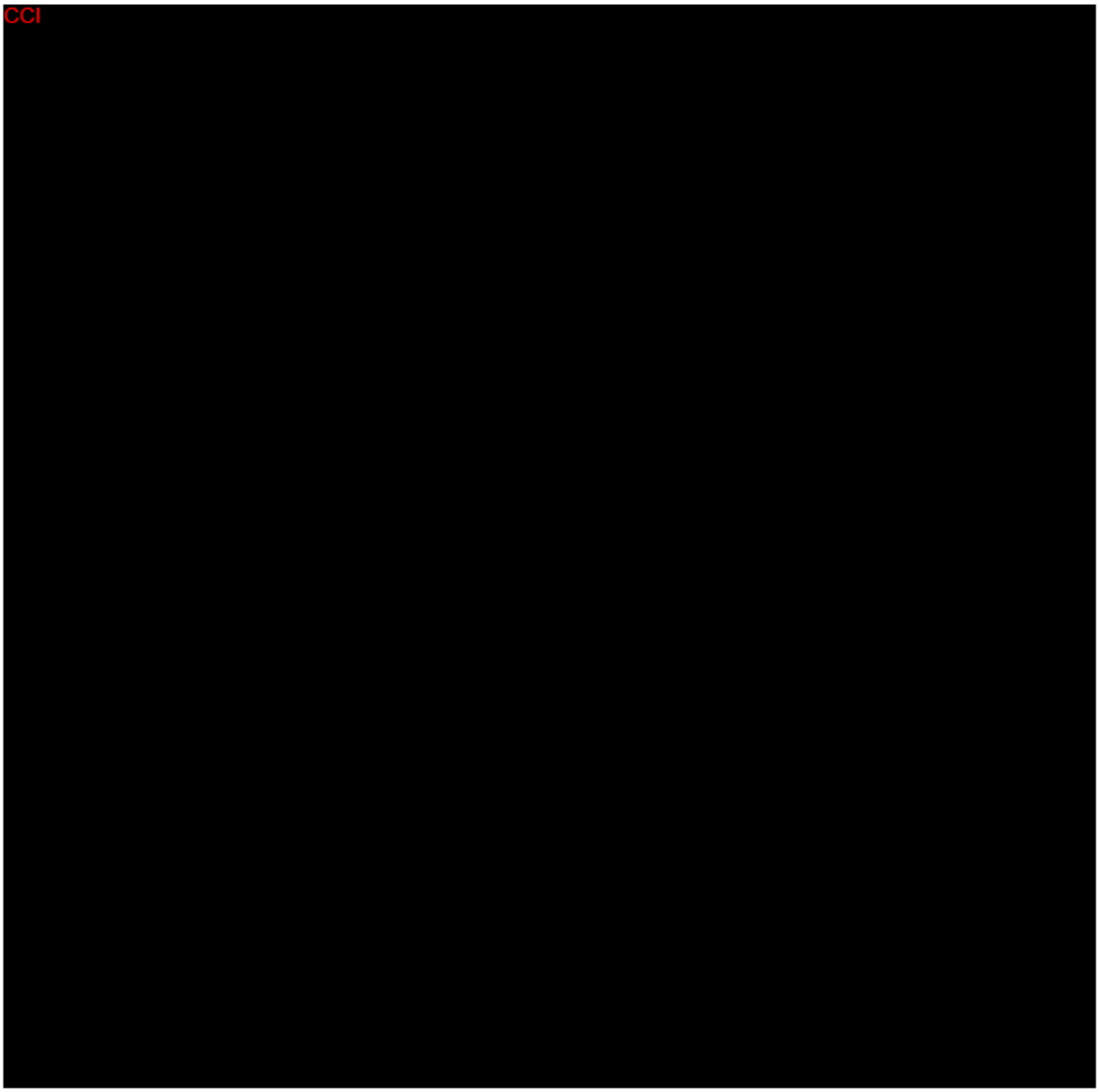

Additional information with descriptions of each study is found in the Investigator's Brochure.

3.5.2. Clinical Experience with TTI-621

As of 01 October 2020, 292 patients have been treated with TTI-621 across two clinical trials, including (a) 235 subjects in Study TTI-621-01: A Phase 1a/1b Trial of TTI-621 in Subjects with Relapsed or Refractory Hematologic Malignancies and Selected Solid Tumors (NCT02663518) and (b) 57 subjects from Study TTI-621-02: A Phase 1 Trial of Intratumoral Injections of TTI-621 in Subjects with Relapsed and Refractory Solid Tumors and Mycosis Fungoides (MF) (NCT02890368).

3.5.2.1. Study TTI-621-01 (Intravenous Route of Administration)

TTI-621-01 is a Phase 1a/b, open-label, multicenter study to evaluate the safety, tolerability, and preliminary efficacy of TTI-621 administered by weekly intravenous infusion. The safety of TTI-621 at doses ranging from 0.05 mg/kg to 0.5 mg/kg was established in an initial dose escalation study and multiple expansion cohorts of subjects with various relapsed/refractory hematologic malignancies and selected solid tumors were enrolled in an expansion phase of the study in which TTI-621 was administered initially at a dose of 0.2 mg/kg; through protocol amendment, higher dose levels of 0.5 mg/kg to 2.0 mg/kg are now under evaluation. Two additional cohorts have also been enrolled to characterize the safety and efficacy of TTI-621 at 0.1 mg/kg in combination with rituximab and in combination with nivolumab. A total of 184 subjects have received TTI-621 as monotherapy, 40 subjects have received TTI-621 in combination with rituximab and 11 subjects have received TTI-621 in combination with nivolumab. The most common diagnoses in these patients is non-Hodgkin lymphoma (NHL; 160 subjects, 68%), Hodgkin lymphoma (HL; 31 subjects, 13%) and AML (20 subjects, 9%).

3.5.2.1.1. Pharmacokinetics

Pharmacokinetic data are available at doses up to 1.4 mg/kg. Preliminary PK data at dose levels of 0.5 to 1.4 mg/kg suggest that TTI-621 serum exposure, as measured by C_{max} and $AUC_{0\text{-}168}$, increases with dose following both single and repeat infusions. The available data suggests that there is no plateau in dose exposure relationship up to 1.4 mg/kg. While the estimated serum half-life of TTI-621 appears to range between 3-4 days, a review of the trough profiles from 0.05 to 1.4 mg/kg suggests that steady state levels of serum TTI-621 exposure are achieved by Week 6+ suggesting that the effective serum half-life of TTI-621 is minimally 3 to 4 days and as long as 7 days.

3.5.2.1.2. Safety

Not unexpected in this patient population, 223/235 subjects (95%) experienced at least one treatment-emergent adverse event. Treatment-emergent adverse events reported for ≥ 20% of subjects were infusion-related reaction (106 subjects, 45%), fatigue (82 subjects, 35%), chills (58 subjects, 25%), pyrexia (53 subjects, 23%), diarrhea (50 subjects, 21%), nausea (50 subjects, 21%) and anemia (49 subjects, 21%). The incidence of treatment-emergent adverse events was generally similar across disease cohorts, although a higher incidence of anemia was reported in the AML cohort compared with the other disease cohorts and the overall study population.

The most frequently-reported treatment-related adverse events of any grade, summarized in Table 1, were infusion-related reaction (103 subjects, 44%), chills (49 subjects, 21%), platelet count decreased (37 subjects, 16%), fatigue (36 subjects, 15%), thrombocytopenia (34 subjects, 14%), anemia (30 subjects, 13%), pyrexia (26 subjects, 11%), nausea (25 subjects (11%), diarrhea (22 subjects, 9%), headache (18 subjects, 8%), vomiting (16 subjects, 7%) and hypotension (13 subjects, 6%). The incidence of treatment-related adverse events was generally similar across disease cohorts, although the incidence of treatment-related anemia was higher in the AML and HL cohorts compared with other disease cohorts and the overall study population.

Table 1. Adverse Events of Any Grade Assessed as Related to Treatment in ≥ 5% of Subjects

Treatment-Related Adverse Event (Preferred Term)	Number of Subjects (Percent)
Any	193 (82%)
Infusion-Related Reaction	103 (44%)
Chills	49 (21%)
Platelet Count Decreased	37 (16%)
Fatigue	36 (15%)
Thrombocytopenia	34 (14%)
Anemia	30 (13%)
Pyrexia	26 (11%)
Nausea	25 (11%)
Diarrhea	22 (9%)
Headache	18 (8%)
Vomiting	16 (7%)
Hypotension	13 (6%)

A total of 91 subjects (39%) experienced a treatment-related adverse event Grade ≥ 3, summarized in Table 2. The most frequently-reported treatment-related Grade ≥ 3 adverse events were platelet count decreased (30 subjects, 13%), thrombocytopenia (23 subjects, 10%) and anemia (20 subjects, 9%). The majority of infusion-related reactions observed across the overall study population were Grade 1 or Grade 2, with only 8 patients (3%) experiencing a Grade ≥ 3 reaction.

Table 2. Adverse Events Grade ≥ 3 Assessed as Related to Treatment in ≥ 2% of Subjects

Grade ≥ 3 Treatment-Related Adverse Event (Preferred Term)	Number of Subjects (Percent)
Any	91 (39%)
Platelet Count Decreased	30 (13%)
Thrombocytopenia	23 (10%)
Anemia	20 (9%)
Infusion-Related Reaction	8 (3%)
Neutropenia	8 (3%)
Neutrophil Count Decreased	7 (3%)
WBC Count Decreased	5 (2%)

A total of 76 subjects (32%) experienced serious adverse events. Treatment-related serious adverse events have been reported for 22 subjects (9%) and are summarized in Table 3. Infusion-related reactions (7 subjects, 3%) and thrombocytopenia (4 subjects, 2%) were the most frequently-reported treatment-related serious adverse events; all other preferred terms were reported for ≤ 2 subjects. Only one infusion-related reaction led to treatment discontinuation; no thrombocytopenia observations led to treatment discontinuation.

Table 3. Serious Adverse Events of Any Grade Assessed as Related to Treatment in ≥ 2 Subjects

Treatment-Related Serious Adverse Event	Number of Subjects (Percent)	Serious Adverse Events Related to Treatment and Resulting in Treatment Discontinuation Number of Subjects (Percent)
Any	22 (9%)	8 (3%)
Infusion-Related Reaction	7 (3%)	1 (0.4%)
Thrombocytopenia	4 (2%)	0 (0%)
Cellulitis	2 (1%)	1 (0.4%)

There have been no deaths related to treatment with TTI-621. At the time of data cut-off, 98 subjects (42%) enrolled in Study TTI-621-01 have died, with 70 of these deaths (71%) due to disease progression. The cause of death was unknown for 14 patients and seven of the 98 deaths (7%) were the result of adverse events that were *unrelated* to treatment with TTI-621 (respiratory failure in two subjects, sepsis in one subject, cardiorespiratory arrest in one subject, cardiovascular disease in one subject, diabetic ketoacidosis in one subject and hypoxemic respiratory failure in one subject). More detailed information about the known and expected benefits and risks and reasonably expected adverse events of TTI-621 may be found in the TTI-621 Investigator Brochure, which is the SRSD for this study.

3.5.2.1.3. Clinical Activity

A summary of responses observed in the intent-to-treat population across all disease cohorts and all dose levels (0.05 – 2.0 mg/kg) in Study TTI-621-01 (reflecting a data cut-off of 01 October 2020) is presented in Table 4. Overall, nine subjects (4%) had complete response (CR) and 21 subjects (9%) had partial response (PR). An additional 84 subjects (36%) achieved stable disease (SD).

Table 4. Summary of Clinical Responses Across Disease Cohorts

Response Category	TCL n=40	PTCL n=21	CTCL n=38	BCL n=21	RTX n=40	HL n=31	AML n=29	Other n=15	Total N=235
CR	1	2	0	0	3	1	2	0	9 (4%)
PR	7	0	3	2	6	3	0	0	21 (9%)
SD	14	3	21	11	14	15	4	2	84 (36%)
PD	10	8	6	6	14	8	19	8	79 (34%)
NA	8	8	6	2	3	4	4	5	40 (17%)
NE	0	0	2	0	0	0	0	0	2 (1%)

TCL (T cell lymphoma), PTCL (peripheral T cell lymphoma), CTCL (cutaneous T cell lymphoma), BCL (B cell lymphoma), RTX (TTI-621+rituximab), HL (Hodgkin lymphoma), AML (acute myeloid leukemia)

Among patients with T cell lymphoma, cutaneous T cell lymphoma or peripheral T cell lymphoma treated with TTI-621 at a dose of 0.2 mg/kg, an overall response rate of 21% has been observed in the intent-to-treat patient population, and a 19% response rate in patients with cutaneous T cell lymphoma at dose levels between 0.7 mg/kg and 2.0 mg/kg, although this portion of the study is ongoing and remains open to enrollment.

Time to response and time on treatment as a surrogate for duration of response are summarized in the form of swimlane plots for patients with PTCL, Mycosis Fungoides and Sézary Syndrome (Figure 4, upper panel) and for patients with DLBCL (Figure 4, lower panel). Only subjects with available response assessment data are included in the figures.

Figure 4. Clinical Responses in Subjects with PTCL, Mycosis Fungoides (MF) and Sézary Syndrome (SS) (upper panel) and DLBCL (lower panel)

3.5.2.2. Study TTI-621-02 (Intratumoral Injection)

TTI-621-02 is a dose-escalation and expansion study was to evaluate the safety, tolerability, pharmacokinetics and anti-tumor activity of TTI-621 administered by intratumoral injection in subjects with relapsed or refractory percutaneously-accessible solid tumors or cutaneous lymphomas. In the dose-escalation phase, nine subjects received a single intratumoral injection of TTI-621 at 1 mg (n=3), 3 mg (n=3) or 10 mg (n=3). Three subjects received intratumoral injections of TTI-621 at a dose of 10 mg given 3 times per week for 1 week (total of three injections) and six subjects received intratumoral injections of TTI-621 at a dose of 10 mg given 3 times per week for two weeks (total of six injections).

No dose limiting toxicities were reported and an maximum tolerated dose was not reached. The maximum assessed dose based on the current formulation of TTI-621 and a 1 mL injection volume was 10 mg administered three times per week for two weeks (total of six injections) and this dose and schedule was taken into expansion cohorts for evaluation as induction therapy as monotherapy or in combination with other anti-cancer agents, including programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitors, pegylated interferon-α2a, talimogene laherparepvec (T-Vec) and local radiation as induction therapy. Following TTI-621 induction therapy, continued weekly treatment with intratumoral TTI-621 was permitted at the Investigator‘s discretion.

A total of 57 subjects were enrolled and treated with TTI-621 in this study: 19 subjects in the dose-escalation part of the study and 38 subjects in the expansion part. A total of 35 subjects (61%) had a diagnosis of cutaneous T-cell lymphoma (CTCL) and 22 subjects (39%) had non-CTCL disease.

A decision was taken not to continue to develop the intratumoral route of administration and study was closed to enrollment with no safety concerns.

3.6. Investigational Medical Product Doxorubicin

Doxorubicin (doxorubicin hydrochloride) is an anthracycline topoisomerase II inhibitor indicated as a component of multi-agent adjuvant chemotherapy for treatment of women with axillary lymph node involvement following resection of primary breast cancer and for the treatment of: acute lymphoblastic leukemia, acute myeloblastic leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, metastatic breast cancer, metastatic Wilms’ tumor, metastatic neuroblastoma, metastatic soft tissue sarcoma, metastatic bone sarcomas, metastatic ovarian carcinoma, metastatic transitional cell bladder carcinoma, metastatic thyroid carcinoma, metastatic gastric carcinoma and metastatic bronchogenic carcinoma.

Refer to the Full Prescribing Information for information on the safety and clinical activity of doxorubicin.

3.7. Rationale for Planned Regimens of Investigational Medical Products

3.7.1. TTI-621

In the dose escalation portion of the study, increasing doses of TTI-621 will be evaluated in combination with fixed-dose doxorubicin in a standard 3+3 dose escalation scheme. The TTI-621 dose escalation will begin with 0.2 mg/kg (Dose Level 1) administered by intravenous infusion over two hours on Day 1 and Day 8 of each 21-day cycle in which doxorubicin is given on Day 1. At the Investigator’s discretion and in the absence of infusion-related reactions in prior cycles, the infusion duration may be reduced to not less than 60 minutes beginning with Cycle 2. The planned dose levels are presented in Table 5.

Table 5. TTI-621 Dose Levels Planned for Evaluation in Combination with Doxorubicin

Dose Level	TTI-621 Dose
1	0.2 mg/kg
2	0.7 mg/kg
3	2.0 mg/kg

If Dose Level 1, 0.2 mg/kg, is found to be intolerable, a lower dose level may be evaluated. If Dose Levels 2 or 3 are not tolerated, intermediate dose levels may be evaluated.

To prevent development of cardiac toxicity, administration of doxorubicin is limited to a maximum of six cycles. Beginning with Cycle 7, TTI-621 will be administered as monotherapy on Day 1 and Day 15 of 28-day cycles until disease progression or development of unacceptable toxicity.

These TTI-621 doses were identified as safe for weekly intravenous administration in study TTI-621-01, in which dose levels ranging from 0.05 to 2.0 mg/kg have been evaluated in over 235 patients to date with a wide range of hematologic and some solid tumor malignancies. Enrollment and follow-up is ongoing in this study, but a preliminary data review shows that the safety profile is very similar across dose levels, with the primary Grade ≥ 3 treatment-related adverse event being acute but reversible thrombocytopenia which occurred in 22% of patients treated at dose levels of 0.05 mg/kg up to 0.5 mg/kg alone and in combinations and in 24% of patients treated at dose levels ranging from 0.5 mg/kg up to 2.0 mg/kg. This thrombocytopenia was found to be transient, occurring within hours after administration and resolving by the next planned weekly infusion. To date, the average treatment duration of TTI-621 given on a weekly infusion schedule is 106 days (range, 1-1094).

3.7.2. Doxorubicin

Doxorubicin is considered standard of care in the intended patient population and will be used in accordance with standard of care with intravenous infusion at a dose of 75 mg/m^2 on Day 1 of each 21-day cycle for a maximum of six cycles (18 weeks). It is intended that each patient will receive six cycles of doxorubicin as fewer than six cycles provides less benefit to the patient compared to six or more cycles[24] and guidelines for prophylaxis for prevention of doxorubicin-mediated dose-limiting neutropenia are provided in Section 5.2.1. Investigators should consult the approved doxorubicin package insert for complete prescribing information (including warnings, precautions, contra-indications, adverse reactions and dose modifications) and may follow institutional procedures for the administration of doxorubicin. Doxorubicin should be made up to a volume of 100 mL and administered through a free-flowing catheter at 75 mg/m^2 by intravenous infusion in less than 60 minutes. The rate of infusion should be decreased if erythematous streaking along the vein proximal to the site of infusion or facial flushing occur.

Doxorubicin is emetogenic and prophylaxis for emesis prior to each infusion of doxorubicin should be given. Institutional guidelines for effective prophylaxis, including specific agents, additional agents and regimens, are acceptable. Cardioprotective prophylaxis must be implemented starting with no later than with initiation of Cycle 5. In accordance with NCCN[26] and ASCO[25] guidelines, all patients should receive prophylaxis with G-CSFs for prevention of febrile neutropenia. Suggested prophylaxis is pegfilgrastim but

other G-CSFs can be considered per the treating physician's discretion; discussion with the Sponsor Medical Monitor is encouraged. Prophylaxis guidelines are provided in Section 5.2.1.

3.8. Benefit-Risk Assessment

Doxorubicin is known to have clinical benefit in patients with soft tissue sarcoma, including leiomyosarcoma, however, with PFS of approximately five months and median overall survival of less than two years,[49-51] there is a significant need for improvement. It is hypothesized that blockade of CD47-mediated immune evasion and concomitant activation of phagocytosis with TTI-621 will be clinically beneficial in patients with sarcoma subtypes in which CD47 is expressed and macrophage scores are increased. In addition, CCI [redacted]

3.8.1. Expected Risks of TTI-621

In clinical trials to date enrolling almost 300 patients with a variety of oncologic indications across a range of TTI-621 dose levels primarily administered by intravenous infusion weekly until progression, TTI-621 has generally been safe and well-tolerated. In TTI-621-01, in which TTI-621 was administered intravenously on a weekly schedule in patients with various relapsed/refractory hematologic malignancies and select solid tumors, the most frequent treatment-related adverse event was infusion-related reaction in 44% of patients. The majority of infusion-related reactions were mild-to-moderate, with only 3% of patients experiencing infusion-related reactions Grade ≥ 3. The infusion-related reactions were reported across all dose cohorts and occurred despite premedication with an anti-histamine and acetaminophen. This study study incorporates a steroid into the prophylaxis regimen, which may be reduced or eliminated at the discretion of the Investigator in patients who do not experience infusion-related reaction.

The most frequent Grade ≥ 3 treatment-related adverse event was acute but reversible thrombocytopenia which occurred in 22% of patients and was not impacted by dose level. The transient decreases in platelet counts occurred in the 24 hours following infusion in the majority of subjects following intravenous exposure to TTI-621, consistent with augmented systemic phagocytic clearance of platelets. In the majority of cases, platelet counts returned to baseline levels within 1 week, enabling continued weekly dosing. No increased risk of bleeding or other clinical sequelae were observed. More detailed information about the known and expected risks and reasonably expected adverse events of TTI-621 may be found in the TTI-621 Investigator Brochure, which is the SRSD for this study.

3.8.2. Expected Benefits of TTI-621

In the early-phase study TTI-621-01 in which TTI-621 was administered by weekly intravenous infusion, a response rate of 13% has been observed, including nine patients with complete response. A clinical benefit rate of 49% has been observed. Among 82 patients with PTCL, Mycosis Fungoides, Sézary Syndrome or DLBCL receiving TTI-621 monotherapy and evaluable for response, 15 responses and an additional 42 cases of disease stabilization were observed. Across these patient groups, 20 patients continued treatment for over 180 days without evidence of disease progression; 10 patients continued treatment for over 270 days without evidence of disease progression seven patients have continued on

treatment without evidence of disease progression for over one year, including one patient with partial response and one patient with complete response that has persisted over 900 days. Thus, it is anticipated that TTI-621 may offer clinical benefit to patients with soft tissue sarcoma, including leiomyosarcoma, and the preclinical data suggesting synergy with anthracycline offers hope that the combination will provide a safe and effective treatment option for this patient population. More detailed information about the known and expected benefits and reasonably expected adverse events of TTI-621 may be found in the TTI-621 Investigator Brochure, which is the SRSD for this study.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Primary Objectives

- Evaluate the safety of escalating dose levels of TTI-621 when administered in combination with 75 mg/m^2 doxorubicin in 21-day cycles and establish the maximum tolerated dose level of TTI-621 when administered in combination with doxorubicin
- Evaluate the safety of selected dose levels of TTI-621 when administered in combination with 75 mg/m^2 doxorubicin in 21-day cycles and then as monotherapy in 28-day cycles until documentation of objective disease progression
- Investigate clinical activity assessed as overall response rate of TTI-621 administered in combination with 75 mg/m^2 doxorubicin for up to six cycles (18 weeks) and then as monotherapy until documentation of objective disease progression

4.2. Primary Endpoints

- Overall safety profile as assessed by the type, frequency, severity, timing and causal relationship of any adverse events, changes in vital signs, ECGs, serum chemistry or other laboratory assessment, treatment delays or discontinuations for patients enrolled into the dose escalation portion of the study
- The percentage of patients with objective response (CR + PR) as defined by RECIST v 1.1 criteria

4.3. Secondary Objectives

- Further assess safety of the selected dose levels of TTI-621 administered in combination with 75 mg/m^2 doxorubicin
- Describe other evidence of clinical benefit

4.4. Secondary Endpoints

- Overall safety profile as assessed by the type, frequency, severity, timing and causal relationship of any adverse events, changes in vital signs, ECGs, serum chemistry or other laboratory assessment, treatment delays or discontinuations for patients enrolled into the selected dose level cohorts in the expansion portion of the study
- Progression-free survival (PFS), overall survival (OS), disease control rate (DCR [CR + PR + SD]), duration of response (DOR), duration of disease control, time to progression and time to new metastases as defined by RECIST v1.1 criteria, time to worsening of ECOG performance status (Appendix A), time to worsening of patient-reporting outcomes assessments

4.5.

CCI

4.6. CCI

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design

This is a multi-center, open-label study designed to evaluate TTI-621 administered in combination with doxorubicin. The first portion of the study will evaluate the safety of increasing dose levels of TTI-621 in combination with doxorubicin at the standard dose of at 75 mg/m^2 in patients with high-grade soft tissue sarcoma who have not received more than one prior line of therapy (gemcitabine with docetaxel) and have not received an anthracycline in any setting (neoadjuvant, adjuvant or as treatment for advanced of metastatic disease). Two dose levels of TTI-621 in combination with doxorubicin will be selected for further evaluation in an expansion phase in which patients with high-grade leiomyosarcoma who have not received more than one prior line of therapy (gemcitabine with docetaxel) and have not received an anthracycline in any setting (neoadjuvant, adjuvant or as treatment for advanced of metastatic disease). Additional key inclusion criteria are ECOG performance status 0-1, age ≥18 years, measurable disease by RECIST v1.1 (expansion cohorts only), and adequate cardiac and end organ function. Patients with prior exposure to anthracyclines will be excluded.

In the Phase I dose escalation portion of the study, the primary objective is assessment of the safety of escalating dose levels of TTI-621 in combination with doxorubicin at the standard dose of 75 mg/m^2. Up to approximately 18 patients are planned to be enrolled in this portion of the study to evaluate three dose levels of TTI-621: 0.2 mg/kg (Dose Level 1), 0.7 mg/kg (Dose Level 2) and 2.0 mg/kg (Dose Level 3). Enrollment will be open to patients with high-grade leiomyosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, dedifferentiated liposarcoma, angiosarcoma and epithelioid sarcoma. Two dose levels will be selected for evaluation in patients with high-grade leiomyosarcoma in the Phase II expansion portion of the study.

The primary objectives of the Phase II expansion portion of the study are continued evaluation of the safety and investigation of clinical activity of the doxorubicin and TTI-621 combination for up to 18 weeks and TTI-621 monotherapy given on an ongoing basis after completion of the 18-week combination in patients with high-grade leiomyosarcoma. Clinical activity will be based on assessment of the overall response rate (ORR by RECIST v1.1 in two 2 expansion cohorts: doxorubicin at 75 mg/m^2 in combination with TTI-621 at a lower dose (Cohort A) and doxorubicin at 75 mg/m^2 in combination with TTI-621 at a higher dose (Cohort B). Up to approximately 31 patients will be treated in each cohort, for a total of approximately 62 patients in this portion of the study.

Secondary objectives include further evaluation of the safety of the combination and assessment of other indications of clinical benefit, including progression-free survival, overall survival, disease control rate, duration of response, duration of disease control, time to progression and time to new metastases as defined by RECIST v1.1 criteria, time to worsening of ECOG performance status, and time to worsening of patient-reporting outcomes assessments.

ORR and CCI [redacted] will be analyzed as an exploratory objective. Other exploratory objectives include CCI [redacted]

CCI [redacted]

The study will consist of a 28-day screening period, a treatment period in which patients will receive doxorubicin in combination with TTI-621 in 21-day cycles for a maximum of six cycles, followed by continued treatment with TTI-621 as monotherapy in 28-day cycles until documentation of objective disease progression or development of unacceptable toxicity, and a long-term follow-up period for assessment of overall survival.

In the combination portion of the study, Cycle 1 through Cycle 6, doxorubicin will be administered after emesis prophylaxis at 75 mg/m^2 on Day 1 of each 21-day Cycle. It is intended that each patient will receive six cycles of doxorubicin as fewer than six cycles provides less benefit to the patient compared to six or more cycles[24] and guidelines for prophylaxis for prevention of doxorubicin-mediated dose-limiting neutropenia are provided in Section 5.2.1. Doxorubicin is administered through a free-flowing intravenous catheter in a volume of 100 mL by infusion over less than 60 minutes; prophylaxis for emesis should be given prior to each infusion and the site may follow institutional guidelines for prophylaxis and infusion as long as they do not contradict this requirement. The rate of infusion should be decreased if erythematous streaking along the vein proximal to the site of infusion or facial flushing occur. As described in Section 5.2.1.1, prophylaxis with dexrazoxane for cardiotoxicity will begin no later than with initiation of Cycle 5 when cumulative doxorubicin will have reached 300 mg/m^2. Because of the potential for cumulative cardiac toxicity, a maximum of six cycles of doxorubicin (18 weeks of treatment) is permitted as per standard of care.

In Cycle 1 through Cycle 6, TTI-621 will be administered by intravenous infusion over 120 minutes on Day 1 and Day 8 of each 21-day cycle. Patients will receive prophylaxis as described in Section 5.2.1.2 on each day of TTI-621 infusion for prevention of possible infusion-related reactions. Beginning with Cycle 2, the infusion period may be reduced to 60 minutes at the investigator's discretion if the patient has not experienced infusion-related reaction. In any cycle in which doxorubicin and TTI-621 are administered on the same day, doxorubicin treatment will precede administration of TTI-621; TTI-621 prophylaxis may begin prior to initiation of doxorubicin administration at the Investigator's discretion.

For the purposes of safety decisions that guide cohort expansion and considerations of TTI-621 dose adjustment in the dose escalation portion of the study, the safety period will consist of the 21-day Cycle 1. Subjects will be considered evaluable for dose-limiting toxicity if they received doxorubicin on Day 1

and TTI-621 on Day 1 and Day 8 of Cycle 1. A patient who withdraws from the study during Cycle 1 in the absence of objective disease progression or dose-limiting toxicity will be replaced. If a dose-limiting toxicity as defined in Section 5.4 is encountered in one patient in the initial three patients in a dose cohort, three additional patients will be enrolled in accordance with the standard 3+3 study design.

After three patients in a dose cohort, or six patients in an expanded dose cohort, complete the 21-day DLT assessment period, the incidence of dose-limiting toxicity, treatment-related safety observations and other available data, such as pharmacokinetic data, will be reviewed by the Sponsor Medical Monitor, Sponsor and Investigators. If no patient in a three-patient cohort or no more than one patient in a six-patient dose cohort experiences treatment-related dose-limiting toxicity, the dose level will be deemed safe and dose escalation may proceed unless there are other safety observations or data that suggest either an expansion of the current dose level or implementation of an intermediate dose level. Thus, three TTI-621 dose levels are anticipated, but additional dose levels may be studied to more closely characterize the combination of TTI-621 with doxorubicin.

After completion of Cycle 6, doxorubicin will be discontinued as per standard of care to avoid development of cumulative cardiac toxicity. However, beginning with Cycle 7, treatment will TTI-621 monotherapy will continue until documentation of progression or unacceptable toxicity; TTI-621 will be administered on Day 1 and Day 15 of 28-day cycles. Patients who are unable to complete the planned six cycles of doxorubicin due to doxorubicin-related toxicity that has occurred despite optimal prophylaxis and medical support and the patient has received at least four cycles of combination treatment may be eligible to begin TTI-621 monotherapy in the next cycle after discussion with the Sponsor Medical Monitor provided the patient is receiving clinical benefit, has not experienced disease progression and TTI-621 re-treatment guidelines as described in Section 9.2.2 are met. The patient may be replace or an additional patient may be enrolled d for the purposes of having a heterogeneous population for evaluation of safety and clinical activity as described in Section 6.7.

Objective disease assessments will be performed after every second cycle of treatment for 50 weeks and after every third cycle thereafter. A patient enrolled in an expansion cohort who withdraws or is withdrawn from the study prior to the first objective disease assessment for a reason other than disease progression or safety will be replaced in order to meet the statistical criteria for the Simon two-stage design. In the event that the LMS diagnosis is not confirmed during central review for a patient enrolled in the dose expansion portion of the study, the patient must be replaced for purposes of meeting the statistical requirements of the study but may be allowed to continue on treatment after discussion with the Sponsor Medical Monitor. Patients who withdraw from the study without evidence of disease progression will be followed in the Long-Term Follow-Up period for documentation of disease progression or initiation of another treatment as well as survival.

The mechanism of immunotherapy is mechanistically distinct from other types of therapy. The patterns of response and progression to immunotherapeutic agents, such as TTI-621, often differ temporally, qualitatively and quantitatively from those observed with cytotoxic and targeted agents. The goal of immunotherapy is to overcome immunosuppression induced by a tumor and its microenvironment, thereby allowing the immune system to develop or activate an immune response that targets and kills

cancer cells. Some patients have experienced pseudo-progression, in which tumor burden showed an initial surge followed by shrinkage, usually at around weeks, that led to development of immune-related disease response criteria that supports continued treatment beyond progression in patients whose clinical conditions have not worsened and who have not experienced severe toxicities. Recognizing that immunotherapy represents a paradigm shift in oncology treatment, patients with an early observation of disease progression but without deterioration in clinical conditions or unacceptable toxicity and who consent should continue treatment until disease progression is verified by a repeated disease assessment at least four weeks later.

Tissue biopsies will be collected during the screening period and after Cycle 2 for patients enrolled in the expansion cohorts; optional biopsies at the time of response and progression will be offered to patients. Serial blood samples will be obtained at baseline, during and after treatment for assessment of TTI-621 pharmacokinetic and pharmacodynamic endpoints as well as CCI

Recognizing that leiomyosarcoma is a rare disease and expecting that patients with leiomyosarcoma may be eager to participate in the study, careful modifications to the enrollment schema have been developed to avoid having to withhold enrollment for these patients. During the dose escalation portion of the study, eligible patients will be enrolled to the cohort that is open at the time they present to the study. Based on known safety of the lowest planned dose of TTI-621, 0.2 mg/kg, gleaned from other ongoing clinical trials, it is anticipated that this dose will serve as the TTI-621 dose level for Cohort A. Thus, expansion Cohort A will open to enrollment once that dose level is judged to be safe in the dose escalation portion of the study; if a dose finding cohort and expansion Cohort A are open to enrollment at the same time, priority for enrollment will be given to the dose escalation cohort and enrollment into expansion Cohort A will be limited to those patients who present to the study after enrollment to a dose escalation cohort is closed and meet all the eligibility criteria for the expansion portion of the study (including documentation of the leiomyosarcoma indication).

When both expansion cohorts are open to enrollment, assignment of eligible patients will be made on an alternating basis, with cohort assignment made by the contract research organization overseeing the study on behalf of the sponsor independent of investigator input and based strictly on chronology of verification of eligibility of patients as they complete screening assessments.

5.2. Doses and Schedule of Administration of Investigational Agents

In Cycle 1 through Cycle 6, patients will receive TTI-621 and doxorubicin. Prophylaxis for known adverse events associated with each agent is required as described below in Sections 5.2.1.1 and 5.2.1.2.

Doxorubicin is administered on Day 1 of each cycle. Doxorubicin treatment is limited to a maximum of six cycles to avoid development of cardiac toxicity. It is intended that each patient will receive six cycles of doxorubicin as fewer than six cycles provides less benefit to the patient compared to six or more cycles[24] and guidelines for prophylaxis for prevention of doxorubicin-mediated dose-limiting neutropenia are provided in Section 5.2.1.

In Cycle 1 through Cycle 6, TTI-621 will be administered on Day 1 after completion of the doxorubicin infusion and on Day 8. For clarity, doxorubicin is not administered on Day 8.

In Cycle 2 through Cycle 6, in the event that doxorubicin dosing is held due to an adverse event from which the investigator believes the patient will recover and continue treament, TTI-621 treatment will also be held. The day on which doxorubicin is re-initiated will then be considered Day 1 of the cycle, and TTI-621 will also be administered as planned on the new Day 1 and subsequent Day 8. Initiation of subsequent cycles will be reset according to the new Day 1.

Beginning with Cycle 7, TTI-621 will be administered as monotherapy on Day 1 and Day 15 of 28-day cycles.

5.2.1. Prophylaxis

5.2.1.1. Doxorubicin Prophylaxis

Doxorubicin is emetogenic and prophylaxis for emesis prior to each infusion of doxorubicin should be given. Institutional guidelines for effective prophylaxis, including specific agents, additional agents and regimens, are acceptable. As described in the following section, TTI-621 prophylaxis includes a requirement for steroid (80 mg oral methylprednisolone or 20 mg intravenous dexamethasone). If site guidelines for doxorubicin prophylaxis include steroid, the steroid dose level should be at least equivalent to that required for TTI-621 prophylaxis as presented in Table 6.

Prophylaxis with dexrazoxane for cardiotoxicity will begin no later than with the initiation of Cycle 5 when cumulative doxorubicin will have reached 300 mg/m^2. Dexrazoxane is administered via intravenous infusion over 15 minutes and should not be administered via intravenous push. The dosage ratio of dexrazoxane to doxorubicin is 10:1 (e.g., 750 mg/m^2 dexrazoxane to 75 mg/m^2 doxorubicin). Do not administer doxorubicin before dexrazoxane; administer doxorubicin 30 minutes after the completion of dexrazoxane infusion.

In accordance with NCCN[26] and ASCO[25] guidelines, all patients should receive prophylaxis with G-CSF for prevention of febrile neutropenia. Suggested prophylaxis is pegfilgrastim but other G-CSFs can be considered per the treating physician's discretion; discussion with the Sponsor Medical Monitor is encouraged.

5.2.1.2. TTI-621 Prophylaxis

Prophylaxis for infusion-related reactions related to administration of TTI-621 will be given prior to infusion of TTI-621 on each day of scheduled treatment. Prophylaxis will consist of acetaminophen, anti-histamine and steroid as described in Table 6. TTI-621 prophylaxis may be initiated prior to doxorubicin infusion on days when doxorubicin and TTI-621 are both given to accommodate site preference and scheduling. While steroid is not required for patients who have not experienced Grade 1 or 2 infusion-related reactions, the Investigator may incorporate steroid into the prophylaxis regimen.

Table 6. Prophylaxis Regimen for TTI-621 to Reduce incidence and/or Grade of Infusion-Related Reaction

Cycle Day of Treatment	Patients Requiring Premedication	Premedication	Administration
Cycle 1 Day 1 Day 8	All patients	80 mg methylprednisolone (oral) OR 20 mg dexamethasone (IV)	At least one hour prior to initiation of TTI-621 infusion
		650 – 1000 mg acetaminophen	At least 30 minutes prior to initiation of TTI-621 infusion
		Anti-histamine (e.g., 50 mg diphenhydramine)	
All subsequent cycles Day 1 Day 8	All patients	650 – 1000 mg acetaminophen	At least 30 minutes prior to initiation of TTI-621 infusion
		Anti-histamine (e.g., 50 mg diphenhydramine)	
	Patients with Grade 3 or Grade 4 IRR in previous infusion[1]	80 mg methylprednisolone (oral) OR 20 mg dexamethasone (IV)	At least one hour prior to initiation of TTI-621 infusion
		650 – 1000 mg acetaminophen	At least 30 minutes prior to initiation of TTI-621 infusion
		Anti-histamine (e.g., 50 mg diphenhydramine)	

[1] Not required for patients who have not experienced Grade 3 or Grade 4 infusion-related reaction, but may be incorporated at the Investigator's discretion.

5.2.2. Doxorubicin

Doxorubicin will be administered with prophylaxis as described in Section 5.2.1.1. In Cycle 1 through Cycle 6, doxorubicin will be used in accordance with standard of care with intravenous infusion at a dose of 75 mg/m^2 on Day 1 of each 21-day cycle for a maximum of six cycles (18 weeks). It is intended that each patient will receive six cycles of doxorubicin as fewer than six cycles provides less benefit to the patient compared to six or more cycles[24] and guidelines for prophylaxis for prevention of doxorubicin-mediated dose-limiting neutropenia are provided in Section 5.2.1. Investigators should consult the approved doxorubicin hydrochloride package insert for complete prescribing information (including warnings, precautions, contra-indications, adverse reactions and dose modifications) and may follow institutional procedures for the administration of doxorubicin. Doxorubicin should be made up to a volume of 100 mL and administered through a free-flowing catheter at 75 mg/m^2 by intravenous infusion in less than 60 minutes. The rate of infusion should be decreased if erythematous streaking along the vein proximal to the site of infusion or facial flushing occur.

In any cycle in which doxorubicin and TTI-621 are administered on the same day, doxorubicin treatment will precede administration of TTI-621. A delay before initiation of TTI-621 is not mandated.

As described below in Section 5.2.3, it is intended that after completion of the planned six cycles of doxorubicin treatment, patients will transition to TTI-621 monotherapy and continue on monotherapy until progression. Patients who are unable to complete the planned six cycles of doxorubicin treatment

due to doxorubicin-related toxicity despite optimal prophylaxis and medical support but have received at least four cycles of combination treatment and are receiving clinical benefit may be eligible to revert to TTI-621 monotherapy with the next cycle (Cycle 5 or Cycle 6) after discusssion with the Sponsor Medical Monitor provided the patient has not experienced disease progression and TTI-621 re-treatment guidelines as described in Section 9.2.2 are met. The patient may be replaced or an additional patient may be enrolled for the purposes of having a heterogeneous population for evaluation of safety and clinical activity as described in Section 6.7. The Investigator may consult with the Sponsor Medical Monitor on a patient-by-patient basis in the event that early evidence of doxorubicin-related toxicity arises.

The dose of doxorubicin should be calculated at the beginning of each cycle.

5.2.3. TTI-621

In Cycle 1 through Cycle 6, following administration of prophylaxis medications as described in Section 5.2.1.2, TTI-621 will be administered by intravenous infusion over 120 minutes on Day 1 and Day 8 of each 21-day cycle. Beginning with Cycle 2, the infusion period may be reduced to 60 minutes at the investigator's discretion if the patient has not experienced infusion-related reaction during prior infusions.

For the purposes of safety decisions that guide cohort expansion and considerations of TTI-621 dose adjustment, the safety period will consist of the 21-day Cycle 1. During the dose escalation portion of the study, dosing of the first patient in a dosing cohort should be followed by a one-week observation period before enrollment of the second and subsequent patients within the dosing cohort.

After completion of Cycle 6, doxorubicin will be discontinued as per standard of care to avoid development of cumulative cardiac toxicity. However, treatment with TTI-621 monotherapy will continue until documentation of progression or unacceptable toxicity. Beginning with Cycle 7, following administration of prophylaxis medications as described in Section 5.2.1.2, TTI-621 will be administered on Day 1 and Day 15 of 28-day cycles.

Patients who are unable to complete the planned six cycles of doxorubicin treatment due to doxorubicin-related toxicity despite optimal prophylaxis and medical support but have received at least four cycles of combination treatment and are receiving clinical benefit may be eligible to revert to TTI-621 monotherapy with the next cycle after discussion with the Sponsor Medical Monitor provided the patient has not experienced disease progression and TTI-621 re-treatment guidelines as described in Section 9.2.2 are met.

The dose of TTI-621 is based on body weight and should be calculated at the beginning of each cycle and may be used throughout the cycle unless a patient experiences a >10% variation in weight within a cycle.

As described previously and presented below in Table 7, three dose levels of TTI-621 are planned to be evaluated in combination with fixed-dose doxorubicin in a 3+3 study design in the dose escalation portion of the study. After review of emergent safety and other data from these dose levels, alternate TTI-621 dose levels may be evaluated to more fully understand safety or pharmacodynamics of TTI-621 in combination with doxorubicin, to more fully identify dose-limiting toxicities, to more clearly define the

maximum tolerated dose, and/or to optimize selection of the most appropriate dose(s) for evaluation in the expansion cohorts.

Table 7. TTI-621 Dose Levels Planned for Evaluation in Combination With Doxorubicin

Dose Level	TTI-621 Dose
1	0.2 mg/kg
2	0.7 mg/kg
3	2.0 mg/kg

During the dose expansion portion of the study, two dose levels of TTI-621 are planned to be evaluated in combination with fixed-dose doxorubicin in 31-patient expansion cohorts in a Simon two-stage model. The low dose of TTI-621 is anticipated to be 0.2 mg/kg and the high dose is anticipated to be the maximum of other TTI-621 dose levels evaluated in the dose escalation portion of the study, prospectively planned to be 2.0 mg/kg, but alternate dose levels may require evaluation and a different dose may be taken forward based after discussion with treating physicians and the Sponsor.

5.3. Criteria for Treatment Discontinuation

Patients may withdraw voluntarily from participation in the study or from study treatment at any time and for any reason. A patient's participation in the study may be terminated at his/her request or on the basis of the Investigator's clinical judgment. The reason for patient withdrawal will be documented in the source data and noted on the electronic case report form (eCRF).

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations at the 30-Day Safety Follow-Up Visit.

If such withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's withdrawal from the study and record the information on the eCRF. If the reason for withdrawal is an adverse event, monitoring should continue until the outcome is evident. The specific event or test result(s) must be recorded in the eCRF. At the discretion of the Sponsor, patients may also be removed from the study.

It should be clearly documented in the source data whether patients withdrew their consent and will not enter the follow-up phase, including objective disease assessment for patients who withdrew from the study in the absence of objective disease assessment and survival, or if patients withdrew their consent for study treatment but will continue further participation in the follow-up phase.

Treatment may be continued until one of the following criteria applies:

- Completion of six cycles of doxorubicin treatment, at which point doxorubicin treatment must be discontinued but the patient may continue with TTI-621 monotherapy
- Objective (radiographic) disease progression: for patients with asymptomatic progression and in the absence of unacceptable toxicity, a consenting patient should continue treatment and a confirmation scan should be conducted at least 4 weeks later to document objective progression prior to removing patient from study treatment

- An unacceptable adverse event or safety observation, such as a persistent moderate toxicity that is intolerable to the patient, that is in the opinion of the Investigator clearly attributed to TTI-621
- An unacceptable adverse event or safety observation, such as a persistent moderate toxicity that is intolerable to the patient, that is in the opinion of the Investigator clearly attributed to doxorubicin and the patient has received fewer than four cycles of doxorubicin. A patient who has completed four cycles of doxorubicin treatment and experiences an adverse event that requires discontinuation of doxorubicin treatment despite optimal prophylaxis and medical support and who is receiving clinical benefit may be eligible to continue on study receiving TTI-621 monotherapy after discussion with the Sponsor Medical Monitor but may be replaced or an additional patient may be enrolled for the purposes of evaluating safety and activity of the combination of doxorubicin and TTI-621 as described in Section 6.7.
- Unacceptable toxicity which in the opinion of the Investigator cannot be attributed to a specific study agent
- Any event which would cause TTI-621 or doxorubicin to be modified by more than two dose reductions or to be held for more than 21 days from the last administered dose and is not attributable to a particular agent of the combination regimen; exception is made for patients who are receiving meaningful clinical benefit and the investigator feels, with Sponsor Medical Monitor concurrence, that continued treatment is in the best interest of the patient
- Any treatment-related adverse event that is deemed life-threatening, regardless of grade; exception is made for patients in whom the life-threatening adverse event is attributed to doxorubicin despite optimal prophylaxis and medical support and the patient is receiving clinical benefit and the patient has received at least four cycles of doxorubicin treatment and the investigator feels, with Sponsor Medical Monitor concurrence, that continuation with TTI-621 monotherapy would be reasonable and the patient meets guidelines for re-treatment with TTI-621 as described in Section 9.2.2
- Discontinuation of TTI-621 treatment
- An intercurrent illness or change in the patient's condition that renders the patient unsuitable for further treatment in the opinion of the Investigator; exception may be made for patients in whom the intercurrent illness or change in condition is thought to render the patient ineligible for continued treatment with doxorubicin despite optimal prophylaxis and medical support and the patient has received at least four cycles of doxorubicin and is receiving clinical benefit and the investigator feels, with Sponsor Medical Monitor concurrence, that continuation with TTI-621 monotherapy would be reasonable and the patient meets criteria for TTI-621 re-treatment as described in Section 9.2.2
- Significant non-compliance with protocol
- Pregnancy
- Withdrawal of consent (patient may participate in long-term assessment of survival and disease status [if withdrawn prior to documentation of objective disease progression] if consent for this portion of the study is not withdrawn)
- Subject is lost to follow-up
- Termination of the study by the sponsor

At the investigator's discretion and in agreement with the Sponsor Medical Monitor, treatment after objective disease progression may continue for a patient who is clinically stable and receiving meaningful clinical benefit and the investigator feels it is in the patient's best interest to continue treatment. The reason for continuing treatment must be thoroughly discussed, agreed with the Sponsor Medical Monitor, and clearly documented in the study files.

5.4. Dose-Limiting Toxicity Criteria for the Dose Escalation Portion of the Study

Dose-limiting toxicity is defined as any of the following treatment-emergent adverse events that occurs during the 21-day Cycle 1 and that are judged by the Investigator as related to TTI-621 or the combination of TTI-621 and doxorubicin. Adverse events that are in the opinion of the Investigator attributable exclusively to intravenous infusion of doxorubicin or any doxorubicin prophylaxis medication will not be considered a dose-limiting toxicity.

CCI

CCI

[redacted]

Infusion-related reactions with TTI-621 are not unexpected and prophylaxis guidelines are provided in Section 5.2.1.2 to mitigate their occurrence and/or severity. While the Investigator may decrease the duration of TTI-621 infusion and/or may decrease or eliminate the steroid component of TTI-621 prophylaxis in a patient who has not experienced infusion-related reaction, caution is urged with respect to implementing both changes simultaneously and a stepwise approach is recommended.

In the event that one patient in a cohort of three patients experiences a dose-limiting toxicity, the cohort will be expanded to a total of six patients. If at least two patients within a dose cohort experience a dose-limiting toxicity during the dose-limiting toxicity period, the conclusion may be drawn that the maximum tolerated dose of TTI-621 in combination with 75 mg/m^2 doxorubicin has been exceeded; any further dose escalation, de-escalation or cohort expansion will be decided in consultation between Investigators, the Sponsor Medical Monitor and the Sponsor after consideration of the particular patients and adverse events experienced, as well as all available safety and pharmacokinetic data of all cohorts.

6. STUDY POPULATION

6.1. Number of Patients

Up to approximately 80 patients are anticipated to participate in the study, with up to 18 in the dose escalation portion of the study and 31 in each of two expansion cohorts. Based on patient outcomes in the dose expansion portion of the study, additional patients may be added to further explore response and/or tolerability of study treatment at one or more dose levels of TTI-621.

6.2. Inclusion Criteria

Patients must meet all the following criteria to be enrolled in the study:

General

1. Written informed consent obtained prior to performing any study-specific procedure, including screening procedures
2. Men and women ≥ 18 years of age
3. ECOG Performance Status 0 or 1
4. Patients enrolled onto the dose expansion cohorts must agree to pre-treatment and on-treatment biopsies if deemed safe and feasible by the treating physician

Disease Characteristics

5. Histologically-confirmed high-grade soft tissue sarcoma that is metastatic or locally advanced and not amenable to curative treatment with surgery or radiation
   - In the dose escalation portion of the study, indications will be limited to high-grade leiomyosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, dedifferentiated liposarcoma, angiosarcoma and epithelioid sarcoma
   - In the expansion portion of the study, enrollment will be restricted to high-grade leiomyosarcoma that is histologically-confirmed at a central laboratory. The patient may be enrolled based on a current or most recent pathology report that provides sufficient detail to support derivation of the histologic interpretation but a pre-treatment tissue specimen must be made available for confirmation during screening or within the first cycle of treatment
6. Objective evidence of disease progression unless disease is newly-diagnosed
7. Measurable disease per RECIST v1.1 (expansion cohorts); target lesions must not be chosen from a previously-irradiated field unless there has been radiographically and/or pathologically documented tumor progression in that lesion prior to enrollment

Organ Function

Adequate organ and hematologic function as defined below:

8. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x ULN; ≤ 5 x ULN in the presence of liver metastasis
9. Serum bilirubin (total) ≤ 1.5 x ULN (≤ 2 x ULN if hyperbilirubinemia is due to Gilbert's syndrome)
10. Serum creatinine ≤ 1.5 x ULN OR creatinine clearance/estimated glomerular filtration rate (eGFR) ≥ 40 mL/min/1.73 m^2 if serum creatinine is > 1.5 x ULN

11. Hemoglobin ≥ 9 g/dL; packed RBC transfusions are not allowed in the week preceding screening evaluation
12. ANC ≥ 1.5 × 10^9/L
13. Platelet count ≥ 100 × 10^9/ L
14. INR ≤ 1.5 x ULN (≤ 2.5 x ULN if on anti-coagulants) and PTT ≤ 5 seconds above the ULN unless receiving anti-coagulation therapy; patients on full-dose anti-coagulation must be on a stable dose of oral anti-coagulant or low molecular weight heparin, have therapeutic INR, no active bleeding (defined as within 14 days prior to first dose of study medication) and no pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices)
15. LVEF determined by echocardiogram or multigated acquisition scan > 50%

Previous Therapy

16. No more than 1 prior treatment regimen for advanced disease, which is limited to gemcitabine with docetaxel
17. Anthracycline-naïve; anthracycline in the neoadjuvant/adjuvant setting renders the patient ineligible for participation
18. Patients who were treated with a prior chemotherapy regimen must have been completed treatment at least three weeks before initiation of study treatment
19. All adverse events from prior treatment must be NCI CTCAE v5 Grade ≤ 1, except alopecia and stable neuropathy, which must have resolved to Grade ≤ 2 or baseline
20. Radiotherapy, including palliative radiotherapy, completed at least two weeks prior to treatment; palliative radiation to non-target lesions while on study is allowed

Contraception

21. Refer to Appendix D for reproductive criteria for male and female patients. Female patients of childbearing potential must have a negative serum beta-human chorionic gonadotropin pregnancy test result at screening and at baseline before the first study drug administration

6.3. Exclusion Criteria

Patients who meet any of the following criteria may not be enrolled:

General

1. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members

Cardiovascular System

2. History of acute coronary syndromes, including myocardial infarction, coronary artery bypass graft, unstable angina, coronary angioplasty or stenting within 24 weeks prior to first administration of study drug
3. History of or current Class II, III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system or symptomatic or poorly-controlled cardiac arrhythmia

4. Uncontrolled or poorly-controlled hypertension (defined as systolic blood pressure >160 mm Hg) for more than four weeks despite optimal medical management

General and Infectious Disease

5. Child-Pugh Class C
6. Any comorbidity or concomitant medical or other condition that in the opinion of the Investigator and/or Sponsor Medical Monitor renders the patient unsuitable for participation in the trial or unlikely or unable to fully comply with study procedures, restrictions and/or requirements that are considered relevant for the evaluation of the efficacy or safety of the trial drug
   Consideration should be given to lack of currently-available immunoprotection against SARS-CoV-2 as a condition that may render a patient unsuitable for participation in the trial or unlikely or unable to fully comply with study procedures, restrictions and/or requirements that are considered relevant for the evaluation of the efficacy or safety of study treatment
7. Uncontrolled intercurrent illness, including active or chronic infection requiring systemic therapy or oral or systemic antibiotics within 14 days prior to study start
8. History of non-viral hepatitis or cirrhosis, alcohol abuse or active tuberculosis
9. Administration of live attenuated vaccines within 28 days prior to start of treatment or anticipated need for vaccination with live attenuated vaccine during the study
10. Major surgery within 28 days of scheduled Cycle 1 Day 1 dosing or minor surgery within seven days prior to initiation of study treatment or elective or planned major surgery to be performed during the course of the clinical trial

CNS Disease Considerations

11. History or evidence of known CNS metastases or carcinomatous meningitis; patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least seven days prior to trial treatment; this exception does not include carcinomatous meningitis which is excluded regardless of clinical stability

Coagulation Considerations

12. Chronic therapy with nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., indomethacin, ibuprofen, naproxen or similar agents) or other anti-platelet agents (e.g., clopidogrel, ticlopidine, dipyridamole, anagrelide); aspirin up to 325 mg per day is permitted
13. Significant bleeding disorders, vasculitis or a significant bleeding episode from the GI tract within three months prior to study entry

Immune System

14. History of severe hypersensitivity reactions to antibodies
15. Systemic steroid therapy (>10 mg daily prednisone or equivalent) or any other form of immunosuppressive therapy within seven days prior to the first dose of study treatment; topical, inhaled, nasal and ophthalmic steroids are not prohibited
16. History of autoimmune disease that has required systemic treatment with disease-modifying agents, corticosteroids, or immunosuppressive drugs unless in the opinion of the investigator the patient is in

a complete and durable remission; physiologic replacement therapies, such as thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, is allowed

17. Prior organ transplantation including allogeneic or autologous stem cell transplantation

Oncology

18. Concurrent or previous other malignancy within two years of study entry with the exception of cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intra-epithelial neoplasm, carcinoma *in situ* of the cervix, or other non-invasive or indolent malignancy
19. Concurrent enrollment in another therapeutic clinical study
20. Prior treatment with anti-CD47 or anti-SIRPα therapy
21. Prior radiation to mediastinal/pericardial region

6.4. Re-Screening

A subject who fails to qualify for the study based on laboratory tests may be considered for re-screening at the discretion of the Investigator and after consultation with the Sponsor Medical Monitor if it is considered that the subject status has changed and the subject may now qualify for the study. Screening is limited to two attempts (initial screening and one re-screening attempt).

6.5. Waivers of Inclusion/Exclusion Criteria

In general, waivers of inclusion or exclusion criteria will not be granted; the Investigator may consult with the Sponsor Medical Monitor on a case-by-case.

6.6. Patients or Partners of Patients of Reproductive Potential

This is an exclusion criterion and women of child-bearing potential must not be considering becoming pregnant during the study.

All women of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of IP and throughout study participation on every woman of childbearing potential. A woman who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

A serum pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the Schedule of Assessments (Table 24). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the patient receiving the study treatment. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the patient must be excluded if the serum pregnancy result is positive.

Patients will be instructed to notify the Investigator if pregnancy is discovered either during or within 45 days of the last dose of study treatment TTI-621 (or as per USPI for doxorubicin combination treatment), which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s).

6.7. Provisions for Enrollment of Additional Patients based on Emerging Data

Because this study has a relatively small sample size and patient heterogeneity may impact on interpretation of safety, clinical activity and/or other study objectives, provision is made that additional patients may be enrolled under certain conditions in order to have a sufficient number of patients to support the planned study objectives.

- It is intended that each patient will receive six cycles of doxorubicin as fewer than six cycles has been shown to provide less benefit to the patient compared to six or more cycles.[24] If emerging data suggests that reduced exposure to doxorubicin has an impact on patient outcome with combined with TTI-621, additional patients may be enrolled to support an evaluation of TTI-621 when combined with doxorubicin for six cycles.
- If emerging data suggests that safety, activity or other study objective is different for patients who have received prior treatment versus no prior treatment, the inclusion criterion may be modified or additional patients may be enrolled to generate a more homogenous patient population.
- If emerging data suggest other patient characteristics may impact on safety, activity or other study objective, additional patients may be enrolled to more fully investigate the observation.

7. ENROLLMENT PROCEDURE AND METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

7.1. Enrollment Procedure

At the time a prospective subject signs the informed consent form, a unique subject number will be assigned and the appropriate portion of a Registration/Enrollment form will be completed and sent to the Sponsor or designee. Subjects will be screened for eligibility according to the criteria outlined in Section 6. Once a subject is deemed eligible, the completed Registration/Enrollment form will be sent to the Sponsor or designee, at which time the TTI-621 dose level and cohort or expansion arm will be assigned.

7.2. Method of Assigning Subjects to Treatment Groups

The dose escalation portion of the study carries a traditional 3+3 design to evaluate three dose levels of TTI-621. Standard guidelines for enrollment for the 3+3 design will be followed, with requirement that three patients complete the 21-day safety assessment period before the next dose cohort is open to enrollment and expansion to six patients in the case of a treatment-related dose-limiting toxicity.

However, recognizing that leiomyosarcoma is a rare disease and expecting that patients with leiomyosarcoma may be eager to participate in the study, careful modifications to the enrollment schema have been developed to avoid having to withhold enrollment for these patients. During the dose escalation portion of the study, eligible patients will be enrolled to the cohort that is open at the time they present to the study. Based on known safety and clinical activity of the lowest planned dose of TTI-621, 0.2 mg/kg, gleaned from other ongoing clinical trials, it is anticipated that this dose will serve as the TTI-621 dose level for Cohort A. Thus, expansion Cohort A will open to enrollment once that dose level is judged to be safe in the dose escalation portion of the study; if a dose escalation cohort and expansion Cohort A are open to enrollment at the same time, priority for enrollment will be given to the dose escalation cohort and enrollment into expansion Cohort A will be limited to those patients who present to the study after enrollment to an escalation cohort is closed and meet all the eligibility criteria for the expansion portion of the study (including documentation of the leiomyosarcoma indication).

When both expansion cohorts are open to enrollment, assignment of eligible patients will be made on an alternating basis, with cohort assignment made by the CRO overseeing the study on behalf of the sponsor independent of investigator input and based strictly on chronology of verification of eligibility of patients as they complete screening assessments.

8. DESCRIPTION OF STUDY TREATMENT

8.1. Description of TTI-621

A description of TTI-621 Investigational Drug Product is provided in Table 8. TTI-621 is a soluble recombinant fusion protein created by combining the CCI human SIRPα (the binding domain for CD47) with the Fc region of human IgG1. CCI

Table 8. TTI-621 Investigational Drug Product Description

Dosage Form	CCI
Unit Dose	TTI-621 with a target protein concentration of CCI mg/mL in CCI mM CCI CCI mM CCI and CCI for Injection, pH CCI
Route of Administration	Intravenous
Physical Description	Protein solution
Storage Conditions	Store frozen at -CCI°C to -CCI°C (CCI°F to CCI°F) or colder

8.2. Description of Doxorubicin

Doxorubicin hydrochloride is an anthracycline topoisomerase II inhibitor. Doxorubicin HCl Injection is supplied in vials containing 10 mg/5 mL, 20 mg/10 mL, 50 mg/25 mL, 150 mg/75 mL, and 200 mg/100 mL doxorubicin HCl as a clear red solution. Doxorubicin hydrochloride for Injection is supplied in vials containing 10 mg, 20 mg, 50 mg, and 150 mg doxorubicin hydrochloride as a red-orange lyophilized powder. Doxorubicin hydrochloridel for Injection is reconstituted with 0.9% Sodium Chloride Injection, USP to obtain a final concentration of 2 mg/mL.

Additional details are provided in the Pharmacy Manual. Sites may follow institutional guidelines for selection of product (Doxorubicin HCl Injection or Doxorubicin Hydrochloride for Injection).

8.3. Preparation and Administration of Study Treatments

All administration of study treatments should be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

8.3.1. TTI-621

As described in Section 5.2.1.2, premedication with acetaminophen, anti-histamine, steroid or a subset of these three agents is required for all subjects prior to each infusion of TTI-621. Modification of the specific agent and/or dosages may be made upon discussion with the Sponsor Medical Monitor.

TTI-621 Drug Product will be CCI and the required dose diluted into CCI mL CCI% CCI for injection USP as further described in the Pharmacy Manual. If not used immediately, the prepared CCI may be stored as described in the Pharmacy Manual. The assigned dose of TTI-621 will be administered intravenously over 120 minutes, although a reduction in duration of infusion to not

less than 60 minutes is permitted after completion of Cycle 1 at the discretion of the Investigator in the absence of infusion-related reaction. 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 flush.

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 on Day 1 of each cycle for purposes of calculating dosage preparation.

Each subject will receive TTI-621 in accordance with the assigned dose until objective assessment of disease progression, unacceptable toxicity or other reason for treatment discontinuation.

In Cycle 1 through Cycle 6, in which TTI-621 is given in combination with doxorubicin, doxorubicin will be administered first. An observation period is not required before initiation of TTI-621 infusion; however, prophylaxis for infusion-related reaction prior to initiation of TTI-621 infusion is required as described in Section 5.2.1.2.

In Cycle 2 through Cycle 6, in the event that doxorubicin dosing is held due to an adverse event from which the investigator believes the patient will recover and continue treament, TTI-621 treatment will also be held. The day on which doxorubicin is re-initiated will be considered Day 1 of the cycle, and TTI-621 will be administered as planned on the new Day 1 and subsequent Day 8. Initiation of subsequent cycles will be reset according to the new Day 1.

8.3.2. Doxorubicin

Doxorubicin is standard of care in this patient population and sites may use institutionally-accepted methods for preparation of doxorubicin for infusion to the patient. Doxorubicin should be made up to a volume of 100 mL and administered through a free-flowing catheter at 75 mg/m^2 by intravenous infusion in less than 60 minutes. The rate of infusion should be decreased if erythematous streaking along the vein proximal to the site of infusion or facial flushing occur. Doxorubicin is emetogenic and prophylaxis for emesis prior to each infusion of doxorubicin should be given as described in Section 5.2.1.1. Institutional guidelines for effective prophylaxis, including specific agents, additional agents and regimens, are acceptable. Cardioprotective prophylaxis must be implemented no later than initiation of Cycle 5 as described in Section 5.2.1.1. In accordance with NCCN[26] and ASCO[25] guidelines, all patients should receive prophylaxis with G-CSF for prevention of febrile neutropenia. Suggested prophylaxis is pegfilgrastim but other G-CSFs can be considered per the treating physician's discretion; discussion with the Sponsor Medical Monitor is encouraged.

8.4. Blinding of Treatment

This is an open-label study; study treatments will not be blinded.

8.5. Treatment Compliance

The study treatments will be administered by personnel at the study site to ensure compliance.

8.6. Study Drug Accountability

Study personnel will maintain accurate records of study treatment shipments, receipts and administration. The site is responsible for the return or destruction of TTI-621 as required.

8.7. Concomitant Medications

Patients are allowed to continue medications that they are taking at baseline. Patients may also receive concomitant medications that are medically indicated as standard care for the treatment of symptoms and intercurrent illnesses. Medications to treat concomitant diseases, e.g., diabetes, hypertension, chronic obstructive pulmonary disease, are allowed. Patients will receive prophylaxis medications to prevent development of infusion-related reactions prior to infusions of TTI-621 and may also receive therapy for symptom control and/or to mitigate side effects of the study medication as clinically indicated, as well as best supportive care as per institutional guidelines. This may include, e.g., anti-emetics, anti-diarrheals, anti-cholinergics, anti-spasmodics, anti-pyretics, anti-histamines, analgesics, antibiotics and other medications such as analgesics, electrolyte replacement, hydration, and/or blood product transfusions intended to treat symptoms. Other prescribed medications for non-neoplastic conditions are allowed, as well as vitamins and nutritional supplements (at doses per the Recommended Dietary Allowance or supplementing a known deficiency). The Investigator should instruct the patient not to take any additional medications (including over-the-counter products) during the study without prior consultation.

Patients must not receive live, attenuated vaccines (e.g., FluMist®) within four weeks prior to first day of study treatment, at any time during the study, or through 90 days after the last dose of TTI-621. Inactivated vaccines are allowed. Influenza vaccination should be given during influenza season only (approximately October to March).

Doxorubicin is a major substrate of cytochrome P450 CYP3A4 and CYP2D6, and P-glycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of CYP3A4, CYP2D6, and/or P-gp (e.g., verapamil), resulting in increased concentration and clinical effect of doxorubicin. Inducers of CYP3A4 (e.g., phenobarbital, phenytoin, St. John's Wort) and P-gp inducers may decrease the concentration of doxorubicin. Concurrent use of inhibitors and inducers of CYP3A4, CYP2D6 or P-gp must be avoided when doxorubicin is being administered.

Due to potential impact on metabolism of both TTI-621 and doxorubicin, THC/CBD and herbal products are prohibited while the patient is receiving treatment on study. The Investigator may discuss specific patients with the Sponsor Medical Monitor.

All concomitant medications, including dose and reason for administration, will be recorded in the eCRF.

8.7.1. Concomitant Corticosteroids

Chronic use of steroid above a daily equivalent dose of 20 mg prednisone is not permitted on study.

8.7.2. Concomitant Hematopoietic Growth Factors and Blood Products

Myeloid growth factors are permitted for treatment-emergent Grade 3 or Grade 4 neutropenia. Likewise, erythropoiesis-stimulating or megakaryopoiesis-stimulating agents may be used for treatment-emergent anemia or thrombocytopenia, respectively. Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

ASCO guidelines for use of WBC growth factors[25] provide that 'prophylactic use of WBC growth factors for prevention of febrile neutropenia is warranted when the risk of febrile neutropenia is approximately 20% or higher and no other equally effective and safe regimen that does not require CSFs is available. Primary prophylaxis is recommended for the prevention of febrile neutropenia in patients who are at high risk on the basis of age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen.' The NCCN guidelines for hematopoietic growth factors[26] classify soft tissue sarcoma treated with doxorubicin as an example of disease setting and chemotherapy regimen with a high risk for febrile neutropenia (>20%) and recommends G-CSF prophylaxis for patients with high risk (>20%) of febrile neutropenia.

Thus, all patients receiving TTI-621 in combination with doxorubicin should receive prophylaxis with G-CSFs for prevention of febrile neutropenia associated with doxorubicin. Suggested prophylaxis is pegfilgrastim and discussion with the Sponsor Medical Monitor regarding the specific agent is encouraged.

8.7.3. Concomitant Anti-Coagulants

Use of selected reversible anti-coagulants (low molecular weight heparin, heparin, warfarin or dabigatran) for prevention or treatment of thrombosis is permitted per the 2017 NCCN guidelines, "Cancer-Associated Venous Thromboembolic Disease", with dose adjustments for thrombocytopenia per local institutional guidelines.

8.8. Treatment of Overdose

There are no known antidotes for overdoses of TTI-621 or doxorubicin. In the event of an overdose of either of these agents, discontinuation of treatment may not have immediate therapeutic effect. In the event of a known or suspected overdose, the patient should be monitored with appropriate hematology and clinical chemistry and should receive supportive therapy, as necessary.

The doxorubin Full Prescribing Information describes some cases of doxorubicin overdose, treatment and outcome. A 58-year-old man with acute lymphoblastic leukemia received 10-fold overdose of doxorubicin (300 mg/m^2) in one day. He was treated with charcoal filtration, hemotopoietic growth factor (G-CSF), proton pump inhibitor and antimicrobial prophylaxis. The patient suffered sinus tachycardia, Grade 4 neutropenia and thrombocytopenia for 11 days, severe mucositis and sepsis. The patient recovered completely 26 days after the overdose. A 17-year-old girl with osteogenic sarcoma received 150 mg of doxorubicin HCl daily for 2 days (intended dose was 50 mg per day for 3 days). The patient developed severe mucositis on Days 4-7 after the overdose and chills and pyrexia on Day 7. The patient was treated with antibiotics and platelets and recovered 18 days after overdose.

Acute overdosage with doxorubicin enhances mucositis, leukopenia and thrombocytopenia. Treatment of a severely myelosuppressed patient require hospitalization, antimicrobials, platelet transfusions and

symptomatic treatment of mucositis. Use of hematopoietic growth factor (G-CSF, GM-CSF) may be considered.

Dexrazoxane may be considered for cardioprotection in patients who have received an excess of doxorubicin.

Decisions regarding dose interruptions or modifications for TTI-621 and/or doxorubicin in the case of a suspected overdose will be made by the Investigator in consultation with the Sponsor Medical Monitor based on the clinical evaluation of the patient.

Information regarding the quantity of the excess dose as well as the duration of the overdosing should be documented in the appropriate eCRF.

9. MONITORING AND MANAGEMENT OF EXPECTED OR POTENTIAL ADVERSE EVENTS

Patient safety will be monitored throughout the study. Documented adverse events observed, mentioned or spontaneously reported by the subject will be documented. The Investigator will be responsible for monitoring the safety of patients and for alerting the Sponsor or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient. The investigator is responsible for appropriate medical care of patients during the study and for adverse events that are serious in nature, considered related or unrelated to the study intervention, or that caused the patient to discontinue before completing the study. The patient should be followed until such an adverse event is resolved or explained.

All laboratory abnormalities and adverse events will be graded according to NCI CTCAE version 5.0.

In the following section, guidelines are presented for management of adverse events attributed to TTI-621 (Section 9.2) or doxorubicin (Section 9.3) and management of adverse events when attribution to neither agent is possible in the opinion of the Investigator (Section 0).

9.1. Prophylaxis for Expected Adverse Events

Prophylaxis for known adverse events associated with doxorubicin or TTI-621 are described in Section 5.2.1. All supportive measures consistent with optimal patient care according to institutional standards should be provided throughout the study. Emergency resuscitation equipment and medications should be readily available. Additional supportive measures should also be available and may include epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators and acetaminophen.

9.2. Management of Adverse Events Associated with TTI-621

9.2.1. TTI-621 Treatment Interruptions

Treatment with TTI-621 may be interrupted for up to 42 days for toxicity; treatment may be interrupted for up to 21 days for reasons unrelated to toxicity if the patient is receiving clinical benefit and after discussion with the Sponsor Medical Monitor. Treatment may be re-instated after discussion with the Sponsor Medical Monitor. In general, if an interruption of more than 42 days is required due to adverse events, TTI-621 will be permanently discontinued; however, if in the judgment of the Investigator, the patient is likely to derive clinical benefit from TTI-621 after a hold of more than 42 days, study drug may be re-started with the approval of the Sponsor Medical Monitor. The infusion duration may be increased and the prophylaxis regimen may be altered after discussion with the Sponsor Medical Monitor, but the TTI-621 dose level does not require modification when administration is re-started. Longer interruptions may be acceptable on a patient-by-patient basis at the discretion of the Investigator after discussion with the Sponsor Medical Monitor.

In Cycle 2 through Cycle 6, in the event that doxorubicin dosing is held due to an adverse event from which the investigator believes the patient will recover and continue treament, TTI-621 treatment will also be held. The day on which doxorubicin is re-initiated will be considered Day 1 of the cycle, and TTI-621 will be administered as planned on the new Day 1 and subsequent Day 8. Initiation of subsequent cycles will be reset according to the new Day 1.

9.2.2. TTI-621 Re-Treatment Guidelines (Initiation of New Cycles of Treatment)

The parameters described in Table 9 should be met for initiation of a new cycle of treatment with TTI-621. Guidelines for intra-cycle dosing, dosing delays and dosing modifications in response to specific treatment-emergent adverse events are provided in Tables 12, 13, 14, 15, 21, 22 and 23.

Table 9. Requirements for Initiation of a New Cycle with TTI-621

Parameter	Criterion
ANC	≥ 1.0×10^9/L
Platelet Count	≥ 75×10^9/L
Bilirubin	≤ 1.5 × ULN
AST, ALT	≤ 3 × ULN (< 5 × ULN if liver metastases)
Treatment-Related Adverse Event	NCI CTCAE Grade < 2 or baseline level (except for alopecia)

9.2.3. TTI-621 Dose Modification Guidelines

The expansion portion of the study is intended to evaluate two dose levels of TTI-621. The lower dose level will be 0.2 mg/kg but the higher dose level is not yet known. Therefore, Table 10 describes modifications for a range of target starting dose levels (Dose Level 1). Provision is not made for treatment with TTI-621 at a dose level below 0.2 mg/kg, but a lower dose level may be allowed after consultation with the Sponsor Medical Monitor for a patient who is receiving clinical benefit and remaining on treatment is, in the opinion of the Investigator, a reasonable treatment option for the patient.

Table 10. TTI-621 Dose Modifications

Dose Level	Dose Level -1	Dose Level -2
2.0 mg/kg	1.4 mg/kg	1.0 mg/kg
1.4 mg/kg	1.0 mg/kg	0.7 mg/kg
1.0 mg/kg	0.7 mg/kg	0.5 mg/kg
0.7 mg/kg	0.5 mg/kg	0.2 mg/kg
0.5 mg/kg	0.2 mg/kg	Discontinue
0.2 mg/kg	Discontinue	Discontinue

9.2.3.1. Infusion-Related Reactions Related to TTI-621 Administration

Infusion-related reactions will be graded as described in Table 11.

Table 11. Definition of Infusion-Related Reaction by CTCAE Grade

CTCAE Grade	Definition
Grade 1 IRR	Mild transient reaction; infusion interruption not indicated; intervention not indicated
Grade 2 IRR	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., anti-histamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours
Grade 3 IRR	Prolonged (i.e., not rapidly responsive to symptomatic medication, brief interruption of infusion, or both); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae
Grade 4 IRR	Life-threatening consequences; urgent intervention indicated

Note: An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritis/itching; rash/desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); vomiting.

As described in Section 5.2.1, prophylaxis is required prior to infusion of TTI-621. Patients will be closely monitored for signs and symptoms of hypersensitivity or allergic reactions. Guidelines for management of infusion-related reactions are presented in Table 12.

Table 12. Management of Infusion-Related Reactions Associated with TTI-621 Administration

CTCAE Grade	Management Guidelines
Grade 1 Infusion-Related Reaction	• The infusion may be stopped or continued at a reduced (50%) infusion rate at the discretion of the Investigator. • If symptoms resolve, the infusion can be re-started or increased, as tolerated, to the baseline rate. • The patient may receive appropriate further treatment for infusion-related reaction if clinically indicated per the site's standard practice for management of IRR.
Grade 2 Infusion-Related Reaction	• The infusion should be stopped. • The patient should receive appropriate further treatment with an anti-histamine and/or acetaminophen if clinically indicated per the site's standard practice for management of IRR. Further medications can be administered if necessary. • Once symptoms have resolved or reduced to Grade 1, the infusion can be continued at a reduced (50%) infusion rate. If after one hour the patient's symptoms do not return and vital signs are stable, the infusion rate may be increased every 30 minutes, as tolerated, to the baseline rate.
Grade 3 Infusion-Related Reaction	• The infusion should be stopped promptly. • The patient must receive appropriate treatment with an anti-histamine and/or acetaminophen and/or methylprednisolone or equivalent and, if necessary, further medications (i.e., epinephrine, bronchodilator). • Only after the complete resolution to Grade ≤1, and after having received appropriate prophylactic medication(s) as described above, the infusion may be resumed at an infusion rate of 25%. If after one hour the patient's symptoms do not return and vital signs are stable, the infusion rate may be increased to a maximum of 50%. • If after the resumption of infusion, symptoms return (irrespective of grade), the infusion must be stopped and the infusion tubing should be disconnected. • The duration of infusion may be prolonged in order to ameliorate IRR but TTI-621 dose does not require reduction.
Grade 4 Infusion-Related Reaction	• The infusion should be stopped promptly and the infusion tubing should be disconnected. • The patient should receive appropriate treatment with an anti-histamine and/or acetaminophen and/or methylprednisolone (or equivalent) and, if necessary, further medications (i.e., epinephrine, bronchodilator). • After discussion with the Sponsor Medical Monitor, the patient must not receive further infusions of TTI-621 if TTI-621 is judged by the Investigator to be the cause of the infusion-related reaction and the investigator feels that implementation of alternative or more aggressive prophylaxis would not be sufficient.

9.2.3.2. Hematologic Adverse Events Related to TTI-621 Administration

Blood counts should be monitored regularly as outlined in Table 24, with additional testing obtained according to standard clinical practice. Management of hematologic adverse events associated with TTI-621 administration is summarized in Table 13, Table 22 and Table 23. Platelet transfusion is allowed to manage severe thrombocytopenia to prevent and minimize bleeding according to ASH and ASCO guidelines. Per these guidelines, the platelet count threshold for prophylactic platelet transfusion is

<10,000 × 10^9/L. Investigators should consider the patient's medical history, concomitant medications and concurrent conditions to provide support for thrombocytopenia.

Table 13. Management of Hematologic Adverse Events Associated with TTI-621 Administration

Note that specific guidelines for management of thrombocytopenia regardless of attribution to TTI-621 and/or doxorubicin are provided in Table 22 and Table 23 and are not described here.

Observation	Management Guidelines
Grade 4 neutropenia lasting > 72 hours	• Delay TTI-621 dosing until the re-treatment criterion (ANC > 1.0 × 10^9/L) is met, then resume TTI-621: ○ At the same dose if dose delay was ≤ 1 week ○ One dose level reduction if dose delay was > 1 week ○ One dose level reduction if the event recurs
Grade 3 febrile neutropenia lasting > 72 hours Grade 3 neutropenia with clinical evidence of infection Grade 4 febrile neutropenia	• Delay TTI-621 dosing until the re-treatment criterion (ANC > 1.0 × 10^9/L) is met, then resume TTI-621 at one dose level reduction
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 was ≤ 1 week ○ One dose level reduction if dose delay was > 1 week ○ One dose level reduction if the event recurs
Grade 4 anemia	• 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 re-treatment criteria

9.2.3.3. Non-Hematologic Events Related to TTI-621 Administration

TTI-621 dose adjustments based on the occurrence of non-hematologic treatment-related adverse events are described in Table 14.

Table 14. Management of Non-Hematologic Adverse Events Associated with TTI-621 Administration

Observation	Management Guidelines
Grade ≥3 events with the following exceptions: • Nausea and/or vomiting lasting <72 hours with supportive care • Fatigue lasting ≤72 hours • Laboratory abnormalities lasting <72 hours and judged by the Investigator as not clinically significant	• For Grade 3 events, delay TTI-621 dosing until the re-treatment criteria are met, then resume TTI-621 at one dose level reduction • 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 re-treatment criteria

9.2.3.4. Management of Other Adverse Events Related to TTI-621 Administration

TTI-621 dose adjustments based on the occurrence of other treatment-related adverse events are described in Table 15.

Table 15. Management of other Treatment-Related Adverse Events

Severity of Event	Management Guidelines
Grade 1	• Maintain TTI-621 dose level • Provide treatment to control symptoms if applicable
Grade 2 (tolerable)	• Maintain TTI-621 dose level • Provide treatment to control symptoms if applicable
Grade 2 (intolerable)	• Hold administration of TTI-621 until the adverse event recovers to Grade ≤ 1 or to baseline level, then resume treatment with TTI-621
Grade 3	• Hold administration of TTI-621 until the adverse event recovers to Grade ≤ 1 or to baseline level, then resume treatment with TTI-621
Grade 4	• Discontinue TTI-621 unless patient is receiving clinical benefit, adverse event recovers to baseline level and treating physician recommends continuation of treatment at a lower dose level or under a modified schedule

9.3. Management of Adverse Events Associated with Doxorubicin

9.3.1. Doxorubicin Treatment Interruptions

Treatment with doxorubicin may be temporarily suspended for up to 42 days to allow for resolution of adverse events. Dose interruptions for reason(s) other than toxicity and re-treatment may be allowed in accordance with standard of care if the patient is receiving clinical benefit and after discussion with the Sponsor Medical Monitor. In general, if an interruption of more than 42 days is required due to adverse events, doxorubicin will be permanently discontinued; however, if in the judgment of the Investigator, the patient is likely to derive clinical benefit from doxorubicin after a hold of more than 42 days, study drug may be re-started with approval of the Sponsor Medical Monitor. Longer interruptions may be

acceptable on a patient-by-patient basis at the discretion of the Investigator after discussion the Sponsor Medical Monitor.

9.3.2. Doxorubicin Re-Treatment Guidelines for Day 1

The laboratory parameters described in Table 16 should be met for re-treatment with doxorubicin.

Table 16. Requirements for Re-Treatment with Doxorubicin on Day 1 (Cycle 2 through Cycle 6)

Parameter	Criterion
Platelets	≥ 75 × 10^9/L
ANC	≥ 1 × 10^9/L
Organ toxicity or other treatment-related adverse event	Grade ≤ 2
Bilirubin	≤ 1.5 × ULN
AST, ALT	≤ 3 × ULN (< 5 × ULN if liver metastases)

9.3.3. Doxorubicin Dose Modification Guidelines

In general, doses should not be reduced for Grade 1 or Grade 2 adverse events, but treatment to manage symptoms should be provided, if applicable.

For the purposes of doxorubicin dose modification in response to adverse events, the dose modification schema presented in Table 17 will be used.

Table 17. Doxorubicin Dose Modifications

Dose Level	Doxorubicin Dose
Dose Level 1	75 mg/m^2
Dose Level -1	60 mg/m^2
Dose Level -2	45 mg/m^2

General guidelines for dose modifications in response to observed adverse events in presented in Table 18. In consideration that doxorubicin is being used as a standard of care anti-cancer therapy in the enrollment patient population and based on Investigator and site experience with doxorubicin in the enrolled patient population, alternate dose modifications may be implemented after discussion with the Sponsor Medical Monitor.

Table 18. Doxorubicin Dose Modification Guidelines

Worst Toxicity in Prior Cycle	Doxorubicin Dose for Next Cycle
Febrile neutropenia Thrombocytopenia with bleeding ANC Grade 4 for ≥ 7 days	Decrease doxorubicin one dose level
Cardiotoxicity, including any signs and symptoms of heart failure, greater than 10% decline in LVEF to below the LLN, greater than 20% decline in LVEF from any level, or LVEF ≤ 45%	Discontinue doxorubicin Consider initiation of dexrazoxane
Grade 3 organ toxicity	Decrease doxorubicin one dose level
Grade 4 organ toxicity	Discontinue doxorubicin
Hepatic impairment Serum bilirubin 1.5 – 3.0 mg/dL Serum bilirubin 3.1 – 5.0 mg/dL Serum bilirubin > 5.0 mg/dL	 50% dose reduction 75% dose reduction Discontinue doxorubicin

9.3.3.1. Cardiac Toxicity Related to Doxorubicin Administration

Cardiotoxicity is a recognized risk of doxorubicin that increases with higher cumulative drug exposure. Cardiac monitoring is conducted by a combination of monitoring of clinical parameters, ECG and echocardiogram (ECHO) / multigated acquisition (MUGA) scan. ECG changes, arrhythmias, tachycardia, and/or chest pain should be managed according to clinical practice based on the specific findings.

Patients will undergo baseline LVEF determination by ECHO or MUGA scan. This evaluation may be repeated at any time during the study if clinically indicated. A decrease in LVEF of ≥ 10% and below the lower limit of normal, or an absolute decrease of 20%, or if the absolute LVEF decreases to or below 40%, doxorubicin will be discontinued. Doxorubicin should also be discontinued if the patient develops Grade ≥ 3 left ventricular systolic dysfunction (symptomatic congestive heart failure).

If doxorubicin is discontinued for the above changes in LVEF despite optimal prophylaxis, the patient may be eligible to continue on study with TTI-621 monotherapy after discussion with the Sponsor Medical Monitor, provided that the patient has completed at least four cycles of doxorubicin therapy, is receiving clinical benefit and meets guidelines for re-treatment with TTI-621.

The diagnostic method used at baseline for cardiovascular assessments (for example ECHO or MUGA scans) should be the same method used throughout the study, unless there is clinical or instrumental evidence that further investigations are needed.

The use of dexrazoxane to reduce the incidence and severity of cardiomyopathy due to doxorubicin administration in patients who have received a cumulative doxorubicin dose of 300 mg/m^2 and who will continue to receive doxorubicin is recommended and will be implemented in this study. As described in Section 5.2.1.1, prophylaxis with dexrazoxane for cardiotoxicity must begin no later than with initiation of Cycle 5 when cumulative doxorubicin will have reached 300 mg/m^2. Do not administer dexrazoxane as a cardioprotectant at the initiation of doxorubicin treatment unless that is the standard of care at a particular institution.

Doxorubicin can result in arrhythmias, including life-threatening arrhythmias, during or within a few hours after doxorubicin administration and at any timepoint during treatment. Tachyarrhythmias, including sinus tachycardia, premature ventricular contractions and ventricular tachycardia, as well as bradycardia may occur. Electrocardiographic changes including non-specific ST-T wave changes, atrioventricular and bundle-branch block can also occur. These electrocardiographic changes may be transient and self-limited and may not require dose modifications of doxorubicin.

9.3.3.2. Secondary Malignancies Related to Doxorubicin Administration

The risk of developing secondary acute myelogenous leukemia and is increased following treatment with doxorubicin. Cumulative incidences ranged from 0.2% at five years to 1.5% at 10 years in two separate trials involving the adjuvant treatment of women with breast cancer. These leukemias generally occur within 1 to 3 years of treatment.

9.3.3.3. Extravasation and Tissue Necrosis Related to Doxorubicin Administration

Extravasation of doxorubicin can result in severe local tissue injury manifesting as blistering, ulceration, and necrosis requiring wide excision of the affected area and skin grafting. When given via a peripheral venous line, infuse doxorubicin over 10 minutes or less to minimize the risk of thrombosis or perivenous extravasation. If signs or symptoms of extravasation occur, immediately terminate the injection or infusion. Extravasation may be present in patients who do not experience a stinging or burning sensation or when blood return is present on aspiration of the infusion needle. If extravasation is suspected, apply ice to the site intermittently for 15 minutes, 4 times a day for 3 days. If appropriate, administer dexrazoxane at the site of extravasation as soon as possible and within the first 6 hours after extravasation.

9.3.3.4. Hematologic Toxicity Related to Doxorubicin Administration

ASCO guidelines for use of WBC growth factors[26] provide that 'prophylactic use of WBC growth factors for prevention of febrile neutropenia is warranted when the risk of febrile neutropenia is approximately 20% or higher and no other equally effective and safe regimen that does not require CSFs is available. Primary prophylaxis is recommended for the prevention of febrile neutropenia in patients who are at high risk on the basis of age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. The NCCN guidelines for hematopoietic growth factors[26] classify soft tissue sarcoma treated with doxorubicin as an example of disease setting and chemotherapy regimen with a high risk for febrile neutropenia (>20%) and recommends G-CSF prophylaxis for patients with high risk (>20%) of febrile neutropenia.

Thus, all patients receiving TTI-621 in combination with doxorubicin should receive prophylaxis with G-CSFs for prevention of febrile neutropenia associated with doxorubicin. Suggested prophylaxis is pegfilgrastim and discussion with the Sponsor Medical Monitor regarding the specific agent is encouraged.

Doxorubicin will not be administered in Cycles 2 – 6 if the patient's ANC is < 1 x 10^9 cells/L or if the platelet count is < 75 x 10^9 cells/L. When necessary, the next treatment cycle should be delayed until the ANC is

≥ 1 x 10^9 cells/L and the platelet count is ≥ 75 x 10^9 cells/L and non-hematologic toxicities have resolved. For patients who experience Grade ≥3 neutropenic fever or infection or Grade 4 neutropenia without fever lasting more than 1 week, doxorubicin should be reduced to 75% of the starting dose (to approximately 60 mg/m^2). If a patient experiences a second incidence of neutropenic fever or infection or has another episode of Grade 4 neutropenia lasting >1 week, then a second dose reduction to 45 mg/m^2 should be implemented. Doxorubicin dose reductions for neutropenia are described in Table 19.

Therapeutic and prophylactic use of G-CSFs will be allowed per current ASCO and NCCN guidelines. For patients with Grade 4 ANC without fever/infection lasting less than one week, re-treatment will be allowed at the Investigator's discretion with the full dose of doxorubicin (75 mg/m^2) with recommended use of G-CSFs per current ASCO guidelines.

Table 19. General Guidelines for Doxorubicin Dose Reduction due to Neutropenia

Observation	Management Guidelines
ANC < 1 x 10^9 cells/L	• Doxorubicin not administered; treatment cycle delayed
At Re-Treatment: • Grade 3 neutropenic fever/infection has occurred • If Grade 4 neutropenia lasting > 1 week has occurred • Grade 4 ANC without fever/infection	• Reduce doxorubicin dose to 60 mg/m^2 • Reduce doxorubicin dose to 60 mg/m^2 • Re-treatment with doxorubicin at full dose at Investigator's discretion with prophylactic G-CSF
Second Incidence of either Grade ≥ 3 neutropenic fever/infection or Grade 4 neutropenia lasting > 1 week	• Reduce doxorubicin dose to 45 mg/m^2

9.3.3.5. Tumor Lysis Syndrome Related to Doxorubicin Administration

Doxorubicin may induce tumor lysis syndrome in patients with rapidly growing tumors and should be managed according to institutional guidelines.

9.3.3.6. Radiation Sensitization and Radiation Recall Related to Doxorubicin Administration

Doxorubicin can increase radiation-induced toxicity to the myocardium, mucosa, skin and liver. Radiation recall, including but not limited to cutaneous and pulmonary toxicity, can occur in patients who receive doxorubicin after prior radiation therapy. Patients should not receive radiation unless there is an urgent or emergent need.

9.3.3.7. Management of Infusion-Related Reactions Related to Doxorubicin Administration

Infusion-related reactions will be graded as described in Table 11 in Section 9.2.3.1. Management of infusion-related reactions associated with doxorubicin administration are described in Table 20.

Table 20. Management of IRR Associated with Doxorubicin Administration

CTCAE Grade	Management Guidelines
Grade 1 or Grade 2	• Slow or stop the infusion rate. • Provide appropriate further treatment for infusion-related reaction if clinically-indicated per the site's standard practice. • If symptoms resolve, the infusion can be re-started or increased, as tolerated, to the baseline rate. • Consider premedications and reduced infusion rate
Grade 3 or Grade 4	• The infusion should be stopped. • Aggressively manage symptoms per the site's standard practice for management of doxorubicin-associated infusion-related reaction. • Re-challenge is discouraged, especially if vital symptoms have been affected. • Consider de-sensitization if therapy is consider essential and patient and physician concur on treatment goals

9.4. Management of Adverse Events not Attributable to a Specific Study Treatment

Guidelines for managing adverse events when attribution to either TTI-621 or doxorubicin is not possible in the opinion of the Investigator are provided in Table 21. Guidelines for management of treatment emergent thrombocytopenia are provided in Table 22 and Table 23 in Section 9.5. Discussion with the Sponsor Medical Monitor is recommended to ensure homogeneity in adverse event management across all patients to the extent possible.

Table 21. General Guidelines for Management of Adverse Events when Attribution is not Possible in the Opinion of the Investigator

Note that guidelines for management of thrombocytopenia are provided in Table 22 and Table 23 in Section 9.5

Observation	Management Guidelines
Hematologic Toxicity[1] • Grade ≥ 3 neutropenia (ANC < 1 x 10^9/L) • Grade ≥ 3 anemia • Hemoglobin < 8 g/dL Non-Hematologic Toxicity[1] Grade ≥ 3 events excluding: • Sub-optimally treated nausea, vomiting, diarrhea • Alopecia • Transient fatigue of a duration consistent with that associated with doxorubicin treatment (1-2 weeks) • Infusion-related reaction in the absence of described prophylaxis • Laboratory abnormalities that are asymptomatic and/or judged by the Investigator as not clinically significant for the patient	First Appearance • Delay study treatment until recovery to Grade ≤ 1 or baseline with ANC > 1.0 x 10^9/L . If no recovery after a delay of > 21 days, discontinue all study treatment. • Reduce doxorubicin and TTI-621 dose levels by one dose level. First Re-Appearance • Delay study treatment until recovery to Grade ≤ 1 or baseline. If no recovery after a delay of > 21 days, discontinue all study treatment. • Reduce doxorubicin and TTI-621 dose levels by one additional dose level. Second Re-Appearance • Discontinue all study treatment.
Hematologic Toxicity • Grade 1 or Grade 2 Non-Hematologic Toxicity • Grade 1 or Grade 2	• No treatment delay • No change in dose level

[1] Interventional or supportive care may be introduced (e.g., G-CSF for neutropenia)

9.5. Guidelines for Management of Thrombocytopenia Assessed as Related to Study Treatment (TTI-621 and/or Doxorubicin)

Guidelines for management of treatment-emergent thrombocytopenia occurring in Cycles 1 – 6 or any cycle when doxorubicin and TTI-621 are administered together are provided in Table 22. Guidelines for management of treatment-emergent thrombocytopenia occuring in Cycles ≥7 or when TTI-621 is administered as monotherapy are provided in Table 23.

Table 22. TTI-621 and Doxorubicin Treatment Guidelines Based on Thrombocytopenia Assessed as Related to Study Treatment in Cycles 1-6 (Combination Treatment)

Platelet Count on Day 8	Management Guidelines
<LLN – 75 x 10^9/L	• Continue TTI-621 and doxorubicin at same dose
<75 x 109 – 50 x 10^9/L	• Continue TTI-621 and doxorubicin at same dose

<50 x 10^9 – 25 x 10^9/L	• Omit TTI-621 on Day 8
	• Monitor platelet recovery (CBC twice weekly recommended)
	• Consider platelet transfusion per ASCO guidelines if clinically indicated
	• On Day 1 of next cycle:
	  ○ if platelets have recovered to ≥ 75 x 10^9/L, initiate cycle with doxorubicin at the same dose and TTI-621 at one dose level reduction
	  ○ if platelets have not recovered to ≥ 75 x 10^9/L, hold doxorubicin and TTI-621 and monitor platelets; initiate the cycle when platelets recover to ≥ 75 x 10^9/L with doxorubicin at same dose and TTI-621 at one dose level reduction
	• In the case of a second occurrence of platelet count decrease to <50 x 10^9, follow the guidelines above or consult with the Sponsor Medical Monitor regarding management
	• The reduced dose of TTI-621 should be used for the remaining combination cycles
	• When the subject completes the combination portion of the study and moves to TTI-621 monotherapy:
	  ○ the original TTI-621 dose level should be re-instated and platelet counts monitored
	  ○ in the case of platelets < 50 x 10^9/L without other causality on Day 15, hold TTI-621 until platelets are ≥ 50 x 10^9/L and then continue with TTI-621 at a one dose level reduction
	  ○ on second occurrence of platelets < 50 x 10^9/L without other causality, reduce TTI-621 by an additional dose level and monitor for tolerability or consult with the sponsor medical monitor regarding management
	  ○ in the absence of disease progression, further dose reductions may be implemented after discussion with the sponsor medical monitor

Platelet Count on Day 8	Management Guidelines
<25 x 10^9/L	• Omit TTI-621 on Day 8 • Monitor platelet recovery (CBC twice weekly recommended) • Consider platelet transfusion per ASCO guidelines if clinically indicated • On Day 1 of next cycle: o if platelets have recovered to ≥ 75 x 10^9/L, reduce doxorubicin and TTI-621 each by one dose level and initiate cycle o if platelets have not recovered to ≥ 75 x 10^9/L, hold doxorubicin and TTI-621 and monitor platelets; initiate the cycle when platelets recover to ≥ 75 x 10^9/L with doxorubicin and TTI-621 each at one dose level reduction • In the case of a second occurrence of platelet decrease to <25 x 10^9/L, consult with the Sponsor Medical Monitor regarding management • The reduced dose levels of doxorubicin and TTI-621 should be used for the remaining combination cycles • When the subject completes the combination portion of the study and moves to TTI-621 monotherapy: o the original TTI-621 dose level should be re-instated and platelet counts monitored o in the case of platelets < 50 x 10^9/L on D15, hold TTI-621 until platelets are ≥ 50 x 10^9/L and then continue with TTI-621 at a one dose level reduction o on second occurrence of platelets < 50 x 10^9/L without other causality, reduce TTI-621 by an additional dose level and monitor for tolerability or consult with the sponsor medical monitor regarding management o in the absence of disease progression, further dose reductions may be implemented after discussion with the sponsor medical monitor.

Day 8 Platelet Count	Management Guidelines
Any platelet count with clinically-relevant bleeding (more than easily-controlled epistaxis, mild gum bleeding or menses)	• Hold TTI-621 on Day 8 • Monitor platelet recovery (CBC twice weekly recommended) • Consider platelet transfusion per ASCO guidelines • On Day 1 of next cycle: o if platelets have recovered to ≥ 75 x 10^9/L and bleeding has resolved, reduce doxorubicin and TTI-621 by one dose level and initiate cycle o if platelets have not recovered to ≥ 75 x 10^9/L and/or bleeding has not resolved, hold doxorubicin and TTI-621 and monitor platelets; initiate the cycle when platelets recover to ≥ 75 x 10^9/L with doxorubicin and TTI-621 each at one dose level reduction • In the case of a second occurrence of platelet count decreased with bleeding attributed to study drug treatment, consult with the sponsor medical monitor regarding management • The reduced dose levels of doxorubicin and TTI-621 should be used for the remaining combination cycles • When the subject completes the combination portion of the study and moves to TTI-621 monotherapy: o the original TTI-621 should be re-instated and platelet counts monitored o in the case of platelets < 50 x 10^9/L on D15, hold TTI-621 until platelets are ≥ 50 x 10^9/L and then continue with TTI-621 at one dose level reduction o on Day 1 of the next cycle, if platelet count remains ≥ 50 x 10^9/L, the reduced TTI-621 dose level should be used for the remainder of the subject's participation. If platelet counts do not remain ≥ 50 x 10^9/L, reduce TTI-621 by another dose level and monitor for tolerability. o in the absence of disease progression, further dose reductions may be implemented after discussion with the Sponsor Medical Monitor.

Table 23. TTI-621 Treatment Guidelines based on Thrombocytopenia Assessed as Related to Study Treatment in Cycles ≥7 (TTI-621 Monotherapy)

Note that these guidelines are intended to address a patient who has not experienced thrombocytopenia in the combination portion of the study but presents with thrombocytopenia during monotherapy treatment.

Day 15 Platelet Count	Management Guidelines
<LLN – 75 x 10^9/L	• Continue TTI-621 at same dose
<75 x 10^9 – 50 x 10^9/L	• Continue TTI-621 at same dose
<50 x 10^9 – 25 x 10^9/L OR Any platelet count with bleeding attributed to study drug treatment	• Monitor platelet recovery (CBC twice weekly recommended) • Consider platelet transfusion per ASCO guidelines if clinically indicated • Hold TTI-621 until platelets are ≥ 50 x 10^9/L and then continue with TTI-621 at a one dose level reduction • On second occurrence of platelets < 50 x 10^9/L without other causality, reduce TTI-621 by an additional dose level and monitor for tolerability; in the absence of disease progression, further dose reductions may be implemented after discussion with the Sponsor Medical Monitor
<25 x 10^9/L	• Monitor platelet recovery (CBC twice weekly recommended) • Consider platelet transfusion per ASCO guidelines if clinically indicated • Hold TTI-621 until platelets are ≥ 50 x 10^9/L and then continue with TTI-621 at a one dose level reduction. • On second occurrence of platelets < 25 x 10^9/L without other causality, reduce TTI-621 by an additional dose level and monitor for tolerability or consult with the Sponsor Medical Monitor regarding management. In the absence of disease progression, further dose reductions may be implemented after discussion with the Sponsor Medical Monitor.

10. STUDY ASSESSMENTS

The procedures and assessments that will be conducted during this study are described in this section and summarized in the Schedule of Assessments (Table 24). Detailed instructions regarding all laboratory procedures, including collection and handling of samples, will be included in the study Laboratory Manual provided by the Sponsor.

The schedule for collection of blood samples for analysis of CCI [redacted] is presented in Table 25. The schedule for collection of samples for CCI [redacted] analyses is presented in Table 26. The schedule for collection of samples for CCI [redacted] analyses is presented in Table 27.

Written informed consent must be granted by each patient prior to the initiation of any study procedure or assessment, including assessment of histology.

Planned timepoints for all safety assessments are provide in the Schedule of Assessments (Table 24). Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 24. Schedule of Assessments

ACTIVITY	Screening	Cycle 1 Day in Cycle 21-day cycle		Cycle 2 – Cycle 6 Day in Cycle (± 1 day) 21-day cycles		Subsequent Cycles Day in Cycle (± 3 days) 28-day cycles		Safety Follow-Up Visit[ff]	Long-Term Follow-Up
	Day -28 to -1	1	8	1	8	1	15		
Informed Consent	X								
Demographics	X								
Inclusion and exclusion criteria	X								
Medical history	X								
Cancer history	X								
Physical exam, vital signs[a]	X	X		X		X		X	
Confirmation of histology in an archival or fresh tissue specimen[b]	X								
Brief physical exam, vital signs[c]			X		X		X		
LVEF[d]	X			X[w]		X[w]		X	
ECOG PS	X	X		X		X		X	
Serum chemistry[e]	X	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X	
Hematology[f]	X	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X	
Coagulation[g]	X	X[t]							
ECG[h]	X	X[t]		X[u]		X[v]		X	
Pregnancy test[i]	X	X		X		X		X	
Radiologic assessment of disease status[j]	X	X						X	X
PRO QoL assessment[k]		X		X		X		X	
Administer doxorubicin with prophylaxis[l]		X		X					
Cardiotoxicity prophylaxis[m]				X[m]					
Administer TTI-621 with prophylaxis[n]		X	X	X	X	X	X		
Adverse events			Ongoing						
Concomitant medications and procedures			Ongoing						

ACTIVITY	Screening	Cycle 1 Day in Cycle 21-day cycle		Cycle 2 – Cycle 6 Day in Cycle (± 1 day) 21-day cycles		Subsequent Cycles Day in Cycle (± 3 days) 28-day cycles		Safety Follow-Up Visit[m]	Long-Term Follow-Up
	Day -28 to -1	1	8	1	8	1	15		
CCI									
Survival, initiation of new anti-cancer therapy[s]									X

[a] Complete physical examination by body system, including vital signs (temperature, blood pressure, pulse rate, respiratory rate, weight, pulse oximetry); height collected during screening only

[b] Expansion phase only and patients with a diagnosis of leiomyosarcoma; to be performed in a central laboratory; patient may be enrolled based on a current or most recent pathology report that provides sufficient detail to support derivation of the histologic interpretation but a pre-treatment tissue specimen must be made available for confirmation during screening or within the first cycle of treatment

[c] Symptom-directed physical examination, with vital signs limited to temperature, blood pressure, pulse rate, respiratory rate

[d] Assessed by transthoracic echocardiogram or MUGA

[e] Glucose, sodium, potassium, calcium, chloride, phosphate, bicarbonate, blood urea nitrogen or urea, creatinine, total protein, albumin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, indirect bilirubin, uric acid, calcium, magnesium, lactate dehydrogenase (LDH)

[f] Hemoglobin, hematocrit, platelets, white blood cells (WBC), neutrophils, lymphocytes, eosinophils, basophils, monocytes, WBC with automated 5-part differential, RBC, absolute reticulocytes, reticulocytes %, MCH, MCV, RDW

[g] International normalized ratio (INR)/prothrombin time (PT), partial thromboplastin time (PTT). To be repeated more frequently if clinically-indicated (e.g., INR/PT for patients on anti-coagulants)

[h] 12-lead ECG, average of triplicate assessments obtained with patient in supine position and within 10 minutes total time; to be performed prior to Cycle 1, Cycle 3, Cycle 4 and Cycle 6; prior to every third cycle beginning with Cycle 7; and at the Safety Follow-Up Visit.

[i] Pregnancy tests will be performed in WOCBP. A serum pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. At baseline and when scheduled at treatment visits, must be performed prior to treatment.

[j] Assessed objectively by CT, MRI or PET/CT; the method used at baseline should be used for the duration of patient participation. Performed every 6 ± 1 week for the first 18 weeks (during combination treatment), every 8 ± 1 week until Week 50 or patient has been on study for one year, and every 12 ± 2 weeks thereafter. CR or PR should be confirmed by repeat assessment at least four weeks after initial observation; treatment can continue during the interval between initial observation and confirmation. In the event that a patient is removed from the study in the absence of radiologic disease progression, a radiologic disease assessment should be performed at the Safety Follow-Up Visit if not performed within the previous four weeks and disease status should be assessed during Long-Term Follow-Up until radiologic demonstration of progression or initiation of new anti-cancer therapy, whichever occurs first

[k] Patient-reported health-related quality of life will be assessed with the EORTC QLQ-C30 tool on Day 1 of every cycle and at the Safety Follow-Up visit prior to initiation of study treatment or other study activities

[l] Doxorubicin should be administered through a free-flowing catheter at 75 mg/m² by intravenous infusion in less than 60 minutes. Prophylaxis against emesis and for prevention of febrile neutropenia should be administered as described in Section 5.2.1.1; additional prophylaxis in accordance with institutional guidelines is acceptable

[m] Cardioprotective administration of dexrazoxane should be initiated no later than initiation of Cycle 5 unless earlier initiation is medically advised or standard of care at a particular institution

[n] Prophylaxis as described in Section 5.2.1.2 will be initiated at least 30-60 minutes prior to initiation of TTI-621 infusion. TTI-621 is administered intravenously over 2 hours. At the Investigator's discretion and in the absence of infusion-related reaction in prior cycles, duration of infusion may be reduced to 60 minutes beginning with Cycle 2. Patients should be observed for one hour after infusion with vital signs assessment in 30-minutes for signs of infusion-related reaction in Cycle 1; the observation period may be reduced at the Investigator's discretion in patients who tolerate the infusion well and do not experience infusion-related reaction.

[o] Detailed sample collection schedule provided in Table 25

[p] Detailed sample collection schedule provided in Table 27

[q] Detailed sample collection schedule provided in Table 26

[r] Detailed sample collection schedule provided in Table 27

[s] Assessed every 12 ± 2 weeks; telephone contact is acceptable

[t] Does not need to be performed if previous assessment was within 72 previous hours

[u] Prior to initiation of Cycle 3, Cycle 4 and Cycle 6; does not need to be performed if previous assessment was within seven days

[v] Prior to initiation of every third cycle (Cycle 7, Cycle 10, Cycle 13, etc.); does not need to be performed if previous assessment was within seven days

[w] Prior to initiation of Cycles 5 and 8; does not need to be performed if previous assessment was previous four weeks

[x] Participants with an unresolved AE considered by the Investigator as possibly related to or associated with [redacted] will be asked to return for [redacted] blood sampling at approximately 3-month intervals (if feasible given the underlying disease) until the last follow-up of the AE up to a maximum of 12 months.

[y] Cycles 2, 3, 4, 5 only

[z] Cycle 2 and Cycle 3 only

[aa] Every second cycle (Cycle 7, Cycle 9, Cycle 11, etc.)

[bb] Cycle 7 only

[redacted]

[dd] May be collected anytime within seven days prior to and 14 days after Cycle 3 Day 1; other times may be acceptable after consultation with Sponsor

[redacted]

[ff] To be performed 30 + five days after last administration of study treatment or before initiation of subsequent anti-cancer therapy, whichever occurs first

Table 25. Sample Collection Schedule for Analysis of CCI

Cycle	CCI
Day of Cycle	
Timepoint(s)	

CCI

Table 26. Sample Collection Schedule for Analysis of CCI

Cycle	CCI
Day of Cycle	
Timepoint	

CCI

Table 27. Sample Collection Schedule for Analysis of [redacted]

	Screening	CCI
CCI		

11. SCHEDULE OF PROCEDURES AND ASSESSMENTS

The following procedures and assessments will be performed at the indicated timepoints.

Screening Visit (Day -28 to -1)

- Informed consent
- Demographics
- Inclusion and exclusion criteria
- Medical history
- Cancer history
- Complete physical examination
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate, weight, pulse oximetry), height
- CCI [redacted]
- LVEF by transthoracic echocardiogram or MUGA
- ECOG PS
- Serum chemistry
- Hematology
- Coagulation
- 12-lead ECG
- Urine or serum pregnancy test (female patients of childbearing potential only)
- Radiologic assessment of disease status using CT, MRI or PET/CT; the method used at baseline should be used for the duration of patient participation
- Blood collection for CCI [redacted]

Cycle 1 Day 1

- Patient-reported quality-of-life assessment
- Complete physical examination
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate, weight, pulse oximetry)
- ECOG PS
- Serum chemistry (unless previous assessment was performed within previous 72 hours)
- Hematology (unless previous assessment was performed within previous 72 hours)
- Coagulation (unless previous assessment was performed within previous 72 hours)
- 12-lead ECG (unless previous assessment was performed within previous 72 hours)
- Urine or serum pregnancy test (female patients of childbearing potential only; must be performed prior to treatment)Administer doxorubicin with prophylaxis
- Administer TTI-621 with prophylaxis
- 60-minute observation period after TTI-621 infusion; vital signs assessed in 30-minute intervals
- Adverse events
- Concomitant medications and procedures
- Blood collection for CCI [redacted]
- Blood collection for [redacted]
- Blood collection for [redacted]

Cycle 1 Day 8

- Brief physical examination
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate)
- Serum chemistry (unless previous assessment was performed within previous 72 hours)
- Hematology (unless previous assessment was performed within previous 72 hours)
- Administer TTI-621 with prophylaxis
- 60-minute observation period after TTI-621 infusion; vital signs assessed in 30-minute intervals
- Adverse events
- Concomitant medications and procedures
- Blood collection for CCI
- Blood collection for

Cycle 2 Day 1

- Patient-reported QoL assessment
- Complete physical examination
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate, weight, pulse oximetry)
- ECOG PS
- Serum chemistry (unless previous assessment was performed within previous 72 hours)
- Hematology (unless previous assessment was performed within previous 72 hours)
- Urine or serum pregnancy test (female patients of childbearing potential only; must be performed prior to treatment)
- Administer doxorubicin with prophylaxis
- Administer TTI-621 with prophylaxis
- Adverse events
- Concomitant medications and procedures
- Blood collection for CCI
- Blood collection for
- Blood collection for

Cycle 2 Day 8

- Brief physical examination
- Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- Serum chemistry (unless previous assessment was performed within previous 72 hours)
- Hematology (unless previous assessment was performed within previous 72 hours)
- Administer TTI-621 with prophylaxis
- Adverse events
- Concomitant medications and procedures
- Blood collection for CCI

Cycle 3 Day 1

- Patient-reported QoL assessment
- Complete physical examination
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate, weight, pulse oximetry)

- ECOG PS
- Serum chemistry (unless previous assessment was performed within previous 72 hours)
- Hematology (unless previous assessment was performed within previous 72 hours)
- Urine or serum pregnancy test (female patients of childbearing potential only; must be performed prior to treatment) 12-lead ECG (unless previous assessment was performed within previous 7 days)
- Radiologic assessment of disease status (unless performed within previous 7 days)
- Administer doxorubicin with prophylaxis
- Administer TTI-621 with prophylaxis
- Adverse events
- Concomitant medications and procedures
- Blood collection for CCI [redacted]
- Blood collection for [redacted]
- Blood collection for [redacted]
- Tissue collection for CCI [redacted]

Cycle 3 Day 8

- Brief physical examination
- Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- Serum chemistry (unless previous assessment was performed within previous 72 hours)
- Hematology (unless previous assessment was performed within previous 72 hours)
- Administer TTI-621 with prophylaxis
- Adverse events
- Concomitant medications and procedures
- Blood collection for CCI [redacted]
- Blood collection for [redacted]

Cycle 4 Day 1

- Patient-reported QoL assessment
- Complete physical examination
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate, weight, pulse oximetry)
- ECOG PS
- Serum chemistry (unless previous assessment was performed within previous 72 hours)
- Hematology (unless previous assessment was performed within previous 72 hours)
- 12-lead ECG (unless previous assessment was performed within previous 7 days)
- Urine or serum pregnancy test (female patients of childbearing potential only; must be performed prior to treatment)
- Administer doxorubicin with prophylaxis
- Administer TTI-621 with prophylaxis
- Adverse events
- Concomitant medications and procedures
- Blood collection for CCI [redacted]
- Blood collection for [redacted]
- Blood collection for [redacted]

Cycle 4 Day 8

- Brief physical examination
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate)
- Serum chemistry (unless previous assessment was performed within previous 72 hours)
- Hematology (unless previous assessment was performed within previous 72 hours)
- Administer TTI-621 with prophylaxis
- Adverse events
- Concomitant medications and procedures

Cycle 5 Day 1

- Patient-reported QoL assessment
- Complete physical examination
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate, weight, pulse oximetry)
- LVEF by transthoracic echocardiogram or MUGA (unless performed within previous 4 weeks)
- ECOG PS
- Serum chemistry (unless previous assessment was performed within previous 72 hours)
- Hematology (unless previous assessment was performed within previous 72 hours)
- Urine or serum pregnancy test (female patients of childbearing potential only; must be performed prior to treatment) Radiologic assessment of disease status (unless performed within previous 7 days)
- Administer doxorubicin with prophylaxis, including cardioprotectant (administration of cardioprotectant must be initiation no later than with Cycle 5, but may be initiated earlier per institutional standard of care)
- Administer TTI-621 with prophylaxis
- Adverse events
- Concomitant medications and procedures
- Blood collection for CCI
- Blood collection for [redacted]
- Blood collection for [redacted]

Cycle 5 Day 8

- Brief physical examination
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate)
- Serum chemistry (unless previous assessment was performed within previous 72 hours)
- Hematology (unless previous assessment was performed within previous 72 hours)
- Administer TTI-621 with prophylaxis
- Adverse events
- Concomitant medications and procedures

Cycle 6 Day 1

- Patient-reported QoL assessment
- Complete physical examination
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate, weight, pulse oximetry)
- ECOG PS
- Serum chemistry (unless previous assessment was performed within previous 72 hours)
- Hematology (unless previous assessment was performed within previous 72 hours)
- 12-lead ECG (unless previous assessment was performed within previous 7 days)
- Urine or serum pregnancy test (female patients of childbearing potential only; must be performed prior to treatment)
- Administer doxorubicin with prophylaxis, including cardioprotectant
- Administer TTI-621 with prophylaxis

- Adverse events
- Concomitant medications and procedures

Cycle 6 Day 8

- Brief physical examination
- Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- Serum chemistry (unless previous assessment was performed within previous 72 hours)
- Hematology (unless previous assessment was performed within previous 72 hours)
- Administer TTI-621 with prophylaxis
- Adverse events
- Concomitant medications and procedures

Cycle 7 and Subsequent Cycles, Day 1

- Patient-reported QoL assessment
- Complete physical examination
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate, weight, pulse oximetry)
- ECOG PS
- Serum chemistry (unless performed within previous 72 hours)
- Hematology (unless performed within previous 72 hours)
- Urine or serum pregnancy test (female patients of childbearing potential only; must be performed prior to treatment)
- Administer TT-621 with prophylaxis
- Adverse events
- Concomitant medications and procedures

Cycle 7, Cycle 9, Cycle 11, etc. Day 1

- Radiologic assessment of disease status (unless performed within previous 7 days)
- Blood collection for CCI [redacted]
- Blood collection for [redacted]
- Blood collection for [redacted]

Cycle 7, Cycle 10, Cycle 13, etc. Day 1

- 12-lead ECG (unless performed within previous 7 days)

Cycle 7, Cycle 11, Cycle 15, etc. Day 1

- Blood collection for CCI [redacted]

Cycle 7 and subsequent cycles, Day 15

- Brief physical examination
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate)
- Serum chemistry (unless performed within previous 72 hours)
- Hematology (unless performed within previous 72 hours)
- Administer TT-621 with prophylaxis

- Adverse events
- Concomitant medications and procedures

Cycle 8 Day 1

- LVEF by transthoracic echocardiogram or MUGA (unless performed within previous 4 weeks)

Safety Follow-Up Visit (30 + 5 days after last administration of study treatment or before initiation of subsequent anti-cancer therapy, whichever occurs soonest)

- Patient-reported QoL assessment
- Complete physical examination
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate, weight, pulse oximetry)
- LVEF by transthoracic echocardiogram or MUGA (unless performed within previous 4 weeks with no abnormalities)
- ECOG PS
- Serum chemistry (unless performed within previous 72 hours)
- Hematology (unless performed within previous 72 hours)
- 12-lead ECG
- Urine or serum pregnancy test (female patients of childbearing potential only
- Radiologic assessment of disease status (unless performed within previous 7 days)
- Adverse events
- Concomitant medications and procedures
- Blood collection for CCI [redacted]

Long-Term Follow-Up

- Radiologic assessment of disease status (patients who have not experienced disease progression)
- Blood collection for CCI [redacted] in participants with an unresolved AE considered by the Investigator as possibly related to or associated with CCI [redacted] at the Safety Follow-Up Visit will be asked to return for CCI blood sampling at approximately 3-month intervals (if feasible given the underlying disease) until the last follow-up of the AE up to a maximum of 12 months.
- Survival (assessed every 12 ± 2 weeks; telephone contact is acceptable)

12. STATISTICAL CONSIDERATIONS

12.1. Sample Size

12.1.1. Dose Escalation

The number of patients will depend on the number of dose cohorts that will be enrolled before reaching the MTD. It is anticipated that three dose levels of TTI-621 given in combination with a fixed dose of doxorubicin will be evaluated and that at least nine and up to approximately 18 patients will be enrolled to evaluate these three dose levels. On this basis of emerging safety data, additional dose levels may be added. The size and design of the dose escalation phase of the study is consistent with standard 3+3 design with the objective of determining the safety of escalating doses of TTI-621 in combination with fixed dose doxorubicin and establishing TTI-621 doses for further evaluation in the intended patient population.

12.1.2. Expansion Cohorts

Expansion cohorts are planned to evaluate two TTI-621 dose levels in combination with doxorubicin: a low dose of TTI-621 (Cohort A) and a higher dose (Cohort B). A Simon two-stage design will be used for each dose cohort, assuming a baseline overall response rate of 10% with doxorubicin monotherapy. In the Simon two-stage design and an alternative of 25%, a power of 90% and one-sided Type 1 error set at 0.20, each dose level cohort will require 18 patients enrolled and evaluable for response in Stage 1; with at least two clinical responses, an additional 13 patients will be enrolled in Stage 2. The combination will be considered worthy of further study if at least five clinical responses are observed in either 31-patient cohort.

12.2. Analysis Populations

The following analysis populations are defined for the study:

Safety population: all patients who received at least 1 dose of TTI-621

Efficacy population: all patients who received at least 1 dose of TTI-621

DLT-evaluable population: all patients who received the full dose of doxorubicin and the planned doses of TTI-621 on Day 1 and Day 8 and have been followed for the entire 21-day DLT period (i.e., Cycle 1) or who have a DLT during Cycle 1 will be considered DLT-evaluable

Response-evaluation population for Simon two-stage design: all patients in either Expansion Cohort A (low dose TTI-621) or Expansion Cohort B (high dose TTI-621) who complete at least two cycles of treatment as described in the protocol and have a post-treatment objective disease assessment unless they were withdrawn prior to meeting this criterion for safety or earlier demonstration of objective disease progression

CCI : all patients who received at least one dose of TTI-621 and have at least one evaluable blood sample for analysis collected

12.3. Criteria for Evaluation

12.3.1. Safety

All patients who receive at least dose of TTI-621 will be included in the safety analyses.

Adverse events, ECGs, LVEF assessments and laboratory data will be summarized and reviewed on an ongoing basis during the study. All adverse events, ECGs, LVEF assessments and safety laboratory abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively by dose cohort and time where appropriate. Absolute value data and changes from baseline data will be summarized as appropriate.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and severity of AEs and laboratory abnormalities will be graded using NCI CTCAE v5 as appropriate. Incidence tables of patients with AEs will be presented for all AEs by maximum severity, SAEs, AEs assessed as related to study drug and adverse events resulting in discontinuation of study drug.

For ECG analyses, the mean of the triplicate ECG parameters will be used as the observation for a patient at a nominal time point. Changes in ECG and laboratory measurements will be summarized.

Listings of all safety data sorted by dose cohort, patient and assessment date will be provided.

12.3.2. CCI

CCI will be evaluated after single and multiple doses of TTI-621 during the course of the study. The CCI of TTI-621, measured as CCI , also will be investigated during the course of the study.

CCI will be listed and summarized at each time point using descriptive statistics; graphical representations will also be provided. Analyses will be performed on the CCI and will be outlined in the Statistical Analysis Plan.

Exploratory analyses may be conducted to evaluate the relationship between TTI-621 end-of-infusion and/or trough concentrations and various efficacy and safety endpoints.

CCI from this study may be pooled with data from other studies and analyzed using population PK approaches. In addition, a model-based approach may be used to explore the potential relationship TTI-621 exposure metrics and efficacy, safety, and/or biomarker endpoints and reported separately.

The CCI will be summarized descriptively. Exploratory analysis may be conducted to evaluate the possible effects of CCI efficacy and safety endpoints.

12.3.3. Clinical Benefit

Clinical efficacy will be evaluated by tumor response for patients with measurable disease as assessed by the Investigators using RECIST v1. 1 (Appendix B). Duration of response will be calculated for patients who achieve a CR or PR and is defined as the time from the date of first documented response (CR or

PR) to the date of documented progression or death after achieving response. Disease control rate is defined as the percentage of patients who have achieved CR, PR, or SD lasting at least 12 weeks.

Clinical activity based on CCI [redacted] will be assessed as an CCI [redacted] of the study.

Patients enrolled in an expansion cohort who withdraw from the study prior to the first objective disease assessment for a reason other than disease progression or safety will be replaced in order to meet the statistical criteria for the Simon two-stage design; these patients will not be included in the response-evaluable population. For a patient enrolled into the dose expansion portion of the study based on local pathology that is not confirmed during central review, the patient must be replaced for purposes of meeting the statistical requirements of the study but may be allowed to continue on treatment after discussion with the Sponsor Medical Monitor.

For patients with asymptomatic progression only or suspected pseudoprogression, the patient may continue treatment beyond progression until a confirmation scan at least four weeks later has confirmed progression.

Efficacy analyses will be based on the efficacy analysis population, i.e. all patients who received at least one dose of study treatment, unless otherwise specified.

12.3.4. Patient-Reported Outcomes

Patient-reported health-related quality of life will be assessed with the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) tool.[53] The PRO measures will be collected on Day 1 of every cycle and at the End-of-Treatment visit. Paper versions of the questionnaire will be used. The questionnaire should be completed prior to initiation of study treatment. Whenever possible, if administration is not possible prior to all other procedures, every effort should be made to administer at the same time point in each visit. Patient-reported questionnaire should be completed by patients when a language translation is available in which the patient is fluent or literate.

Broadly used in cancer trials, validated, and available in over 80 different languages, the EORTC QLQ-C30 is a reliable and validated tool. The EORTC QLQ-C30 is a self-administered, self-reported general cancer-specific questionnaire consisting of 30 items covered by one of three dimensions:

- Global health status/ (two items)
- Functional scales (15 total items addressing either physical, role, emotional, cognitive or social functioning)
- Symptom scales (13 total items addressing either fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial impact)

The recall period is the past week and completion time is typically five to seven minutes. The questionnaire will be scored as described by the EORTC scoring manual.[54]

12.3.5. CCI

[redacted]

12.4. Statistical Methods

Tabular summaries of data will be descriptive in nature (i.e., number of patients [n], mean, standard deviation, median, minimum and maximum for continuous variables and n and percent for categorical variables). For efficacy parameters, including objective response rate and disease control rate, 95% confidence intervals will be presented using the Wilson's score method.

Protocol deviations will be listed. Protocol deviations that might substantially affect efficacy analyses will be determined prior to database lock.

A more detailed description of analysis methods will be provided in the SAP to be completed prior to the clinical database lock.

13. SAFETY

Adverse events observed, mentioned on open questioning by a member of the Investigator team or spontaneously reported by the subject will be documented. Adverse events will be documented event based. The observation phase for adverse events will start with signing the informed consent and will end at the completion of the active reporting period**.** Planned timepoints for all safety assessments are provided in the Study Assessments (Section 10). Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

13.1. Definition of Adverse Events

13.1.1. Adverse Event

An adverse event is any untoward medical occurrence or the worsening of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. Development of new disease lesions or disease progression is not considered an adverse event.

All AEs and SAEs occurring in a patient during the active collection period as described in Section 13.5.3. will be recorded on the appropriate CRF from the signature of the informed consent. All SAEs must be reported on the CT SAE Report Form to Pfizer Safety immediately upon awareness and under no circumstance should this exceed 24 hours. A worsening of a condition/disease recorded in the medical history is reportable as an AE. Documentation must be supported by an entry in the patient's source medical records. Laboratory abnormalities requiring treatment or considered by the investigator to be clinically relevant should be reported in the CRF as an AE. Each AE is to be evaluated for duration, severity and causal relationship with the IP.

For the purposes of this study, events that are unequivocally due to disease progression should not be reported as AEs unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study, the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 if it occurs during the active collection period. 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 SAE criteria. New cancers are those that are not the primary reason for study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

13.1.2. Serious Adverse Event

A serious adverse event is an adverse event occurring during any study at any dose of the investigational product(s) that fulfills one or more of the following:

- Results in death

- Is immediately life-threatening (the subject was at risk of death at the time of the event; this does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

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 patient 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.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

All serious adverse events that occur after any patient has signed informed consent, been enrolled, before treatment, during treatment, or within 30 days following the cessation of treatment, whether or not they are related to the study intervention, must be recorded on a Serious Adverse Event form.

13.2. Clarifications to Serious Adverse Event Reporting

- Death is an outcome of a serious adverse event and not a serious adverse event in itself. When death is an outcome, report the event(s) resulting in death as the serious adverse event term (e.g., “pulmonary embolism”). If the cause of death is unknown, report “Death, unknown cause” as the serious adverse event term.
- Pre-planned or elective hospitalizations including social and/or convenience situations (e.g., respite care) are excluded from serious adverse event reporting. In addition, emergency room visits and admission under 23-hour observation are excluded from serious adverse event reporting; however, such events should still be reported on the appropriate adverse event eCRF page.
- An isolated laboratory abnormality is not reportable as a serious adverse event unless the Investigator assesses that the event meets the standard ICH criteria for a serious adverse event.

13.3. Assessment of Causality

The relationship of each adverse event to administration of the study drug(s) will be assessed by the Investigator after careful consideration of all relevant factors such as (but not limited to) the underlying study indication, co-existing disease, concomitant medication, relevant history, pattern of the adverse event, temporal relationship to receipt of the study medication(s) and de-challenge or re-challenge.

Study drug or study treatment refers to intravenously-administered doxorubicin and intravenously-administered TTI-621. The assessment of relationship to study drug or study treatment will be done for

each drug separately. If the Investigator feels such a distinction cannot be made, the assessment will be based on the combination of the two drugs.

The assessment of causality is based on the question of whether there was a reasonable causal relationship to the study drug in question according to the following guidelines:

RELATED (possible, probably or definitely related): there is a reasonable possibility that the study treatment caused the event; one or more of the following criteria apply:

- The event follows a reasonable temporal sequence from administration of study treatment
- The event could not be reasonably attributed to the known characteristics of the patient's clinical state, environment or toxic factors or other modes of therapy administered to the patient
- The event follows a known pattern of response to study treatment
- The event disappears or decreases on cessation or reduction in dose of the study treatment. In some situations, an AE will not disappear or decrease in intensity upon discontinuation of the study treatment despite other clear indications of relatedness

UNRELATED (unlikely related or definitely not related): There is no reasonable possibility that the study treatment caused the event; one or more of the following criteria apply:

- The event does not follow a reasonable temporal sequence from administration of study treatment
- The event could be reasonably attributed to known characteristics of the patient's clinical state, concurrent illness, environment or toxic factor or other therapies administered to the patient
- The event does not follow a known pattern of response to study treatment
- The event does not disappear or decrease on cessation or reduction in dose of the study treatment, and it does not reappear or worsen when the study treatment is re-administered
- There is a clear alternative explanation

13.4. Assessment of Severity

The severity rating of an adverse event refers to its intensity. The severity of each adverse event will be categorized using the NCI CTCAE v5. For any term that is not specifically listed in the CTCAE scale, intensity should be assigned a grade of 1 through 5 using the following CTCAE guidelines:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to adverse event

It is important to distinguish between serious adverse events and severe adverse events. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 13.1.2. An adverse event of severe intensity may not be considered a serious adverse event.

13.5. Action Taken

Any action with study treatment to resolve the adverse event is to be documented using the categories listed below. The study drug action should be recorded separately for each component as detailed in the eCRF.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Not applicable
- Unknown

13.5.1. Other Specific Treatments of Adverse Event

- None
- Remedial drug therapy
- Other

13.5.2. Outcome of Adverse Event

The outcome of the AE is to be documented as follows:

- Recovered / resolved
- Recovering / resolving
- Recovered / resolved with sequelae
- Not recovered / not resolved
- Fatal
- Unknown

13.5.3. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each patient begins from the time the patient provides informed-consent, which is obtained before undergoing any study-related procedure and/or receiving study intervention, through and including a minimum of 30 calendar days after the last administration of the study intervention.

For patients who are screen failures, the active collection period ends when screen failure status is determined.

If the patient withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a patient permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek information on AEs or SAEs after the patient has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has completed the study, and they consider the event to be reasonably related to

the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

13.5.4. Documentation

All AEs (serious and non-serious) occurring within the period of observation for the study must be documented in the CRF with the following information, where appropriate. (The period of observation for the study is described in Section 13.5.3).

- AE name or term
- When the AE first occurred (start date)
- When the AE stopped (stop date or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to the IP(s)

All nonserious AEs and SAEs occurring in a patient during the active collection period which begins after obtaining informed consent as described in Section 13.5.3, will be recorded on the AE section of the CRF.
The investigator or designee is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the patient.

The investigator must record his or her reasoning for this decision in the patient's medical record and as a comment on the CRF

Reporting of AEs and SAEs for patients who fail screening are subject to the CRF requirements as described in Section 13.5.3.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

If a patient begins a new anti-cancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above indicated active collection period. Note that a switch to a commercially available version of the study intervention is considered as a new anti-cancer therapy for the purposes of SAE reporting.

13.5.5. Follow-Up

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

If a patient is lost to follow-up, this should be captured accordingly within the adverse event eCRF and on the follow-up serious adverse event report

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

All findings relevant to the final outcome of an AE must be reported in the patient's medical record and recorded on the eCRF page

New and ongoing treatment-related serious adverse events should be followed beyond the 30-day Safety Follow-Up Visit. If the patient dies, this should be captured as the outcome of the adverse event unless no link between the adverse event and the patient death can be established, in which case the adverse event will be marked as ongoing and the death will be reported as a separate event. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

13.5.6. Notification

Serious Adverse Events

The investigator or designee must report all SAEs (related and unrelated) promptly to Pfizer Safety within 24 hours of the knowledge of the occurrence.

To report the SAE, complete the CT SAE form electronically in the Pfizer SAE Submission Assistant (PSSA) tool. When the form is completed, Pfizer Safety personnel will be notified electronically. If the event meets serious criteria and it is not possible to access the PSSA tool, then fax the completed paper CT SAE form to Pfizer Safety within 24 hours of awareness. When the PSSA tool becomes available, the SAE information must be entered within 24 hours of the PSSA system becoming available.

At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Patient's study number
- Patient's year of birth
- Patient's gender
- Date of first dose of IP(s)

- Date of last dose of IP(s), if applicable
- AE term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to IP(s). ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

13.5.7. Regulatory Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of patients and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

13.5.8. Adverse Events of Special Interest

The following events are considered AEs of special interest based on preclinical toxicology studies with TTI-621. Additional details are provided in the current version of the IB for TTI-621.

- Infusion-related reaction
- Thrombocytopenia
- Hemorrhage
- Anemia

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that these pre-specified events

occur more frequently than expected, e.g., based on epidemiological data, literature or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOPs.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 13.5.4 and 13.5.6. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

13.5.9. Lack of Efficay

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety only if associated with an SAE.

13.5.10. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a patient receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members and others who may be exposed. An environmental exposure may include Exposure During Pregnancy (EDP), Exposure During Breastfeeding (EDB) and occupational exposure.

Any such exposure to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

Exposure During Pregnancy (EDP)

An EDP occurs if:

- A female patient is found to be pregnant while receiving or within 45 days after discontinuing study intervention TTI-621 (for combination therapy, consult the Doxorubicin USPI).
- A male patient who is receiving or has discontinued study intervention inseminates a female partner prior to or around the time of conception (not applicable for TTI-621 as is known not to be transmitted through semen; for combination therapy, consult the applicable product label).
- A female nonpatient is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation or skin contact then inseminates his female partner prior to or around the time of conception (not applicable for TTI-621 as is known not to be transmitted through semen; for combination therapy, consult the Doxorubicin USPI).

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- EDP occurs in a patient or patient's partner, the investigator must report this information to Pfizer Safety through PSSA, regardless of whether an SAE has occurred. Details of the pregnancy in a patient will be collected after the start of study intervention (TTI-621 or combination therapy) or patient's partner (combination therapy) and until 45 days after the last dose of TTI-621 (consult relevant product label for combination therapies).
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety through PSSA using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the patient enrolled in the study, the information is not recorded on a CRF.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

Exposure During Breastfeeding (EDB)

An EDB occurs if:

- A female patient is found to be breastfeeding while receiving or after discontinuing study intervention
- A female non-patient is found to be breastfeeding while being exposed or having been exposed to study intervention (i.e., environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion, inhalation or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported through PSSA. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the patient enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form (extracted from PSSA) is maintained in the investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safey within 24 hours of the investigator's awareness through PSSA, regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a patient enrolled in the study, the information is not recored on a CRF; however, a copy of the completed CT SAE Report Form (extracted from PSSA) must be maintained in the investigator site file.

13.5.11. Medication Error

Medication errors may result from the administration or consumption of the study intervention by the wrong patient, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving participant exposure to the study intervention
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant
- The administration of expired study intervention
- The administration of an incorrect study intervention
- The administration of an incorrect dosage
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error and associated AE(s), serious and non-serious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours through PSSA only when associated with an SAE.

13.6. Laboratory Abnormalities

To the extent possible, all laboratory abnormalities observed during the course of the study will be included under a reported adverse event term describing a clinical syndrome (e.g., elevated blood urea nitrogen and creatinine in the setting of an adverse event of "renal failure"). In these cases (e.g., an adverse event of renal failure), the laboratory abnormality itself (e.g., elevated creatinine) does not need to be recorded as an adverse event.

If a laboratory abnormality cannot be reported as a clinical syndrome, AND if the laboratory abnormality results in a therapeutic intervention (i.e., concomitant medication or therapy), is a dose-limiting toxicity or is judged by the Investigator to be of other particular clinical relevance, then the laboratory abnormality should be reported as an adverse event. Laboratory Abnormalities requiring treatment or considered by the Investigator to be clinically-relevant should be reported inthe CRF as an AE.

See Appendix E for suggested actions and follow-up assessments in the event of potential Drug Induced Liver Injury (DILI).

See Appendix F for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

Patients experiencing adverse events or clinically-significant laboratory abnormalities will be assessed and appropriate evaluations performed until all parameters have returned to baseline levels or are consistent with the patient's then-current physical condition.

13.7. Sponsor Safety Review

The Medical Monitor or designee will be responsible for the ongoing review and evaluation of safety throughout the study (this includes all laboratory, ECG and echocardiogram/MUGA data as well as all adverse events).

13.8. Overview of Safety Monitoring

Throughout the study, investigators, site staff and the study Sponsor will meet regularly to review the status of all active patients on study. During the dose escalation portion of the study, a weekly safety and information call will be held with participating investigators and site staff to discuss safety, review any questions, provide updates and to share information across sites. At the completion of each dose escalation cohort, safety data will be summarized and presented for discussion with all investigators for the purpose of determining whether the observed safety in each cohort warrants escalation to the next higher dose level or whether an alternate dose level or other action should be considered.

During the dose expansion portion of the study, these regularly-scheduled safety and information calls will continue; the calls will initially be held at two-week intervals although *ad hoc* meetings may be held

as necessary to review specific safety or other issues that might arise during the course of the study. As the study progresses, the frequency of these safety and information calls may be adjusted to reflect need on the basis of safety observations observed, the rate of enrollment and investigator or Sponsor request or need.

14. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

This study will be conducted in accordance with applicable national and local regulations and guidelines, Good Clinical Practice (GCP), including 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). The Investigator's signature on the Principal Investigator Acknowledgement Form (Appendix G) documents each Investigator's commitment to this requirement.

14.1. Regulatory Authority Approvals

The Sponsor or designee will submit the study protocol plus all relevant study documents to applicable regulatory agencies for approval before the study start. No patient will be admitted to the study until appropriate regulatory approval of the study protocol has been received.

Each Investigator must complete a Form FDA 1572 or equivalent and provide the completed form according to written instructions to the Sponsor (or designee). Each Investigator must submit to the Sponsor (or designee) financial disclosure information according to national law and/or local regulations.

Data generated in the US will be handled in accordance with the Health Information Portability and Accountability Act (HIPAA). The study will be registered at www.clinicaltrials.gov using the Protocol Registration System.

14.2. Institutional Review Board

This protocol and any material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the Investigator to an IRB. This also applies to protocol amendments.

The Sponsor will supply relevant data for the Investigator to submit the study protocol and additional study documents to the IRB. The Principal Investigator will submit the study protocol for review and approval by an IRB, according to national law and/or local regulations, and will provide the IRB with all appropriate materials.

Verification of the IRB's unconditional approval of the study protocol and the written ICF will be transmitted to the Sponsor. This approval must refer to the study by exact study protocol title and number, identify the documents reviewed, and state the date of the review.

No patient will be admitted to the study until appropriate IRB approval of the study protocol has been received, the Investigator has obtained the signed and dated ICF, and the Sponsor is notified.

The Principal Investigator will submit appropriate reports on the progress of the study to the IRB at least annually in accordance with applicable national law and/or local regulations and in agreement with the policy established by the IRB and Sponsor.

The IRB must be informed by the Principal Investigator of all subsequent study protocol amendments and of serious adverse events or SUSARs occurring during the study that are likely to affect the safety of the patients or the conduct of the study.

14.3. Confidentiality of Information

The Investigator must ensure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. Only patient initials and an identification code (i.e., not names) should be recorded on any form submitted to the Sponsor and the IRB. The Investigator must keep logs on screened and enrolled patients. In addition, the Investigator must have a list where the identity of all treated patients can be found.

The Investigator agrees that all information received from the Sponsor, including, but not limited to, the Investigator's Brochure, this protocol, eCRFs, the protocol-specified treatment, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain. The Investigator shall be under additional obligations related to non-disclosure confidential information and the handling of intellectual property as set forth in the Clinical Trial Agreement.

14.4. Patient Informed Consent

All information about the clinical study, including the patient information and the informed consent form, is prepared and used for the protection of the human rights of the patient according to ICH GCP guidelines and the Declaration of Helsinki.

It is the responsibility of the Investigator to obtain signed informed consent forms from each patient participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures.

The informed consent form, prepared by the Investigator with the assistance of the Sponsor, must be approved along with the study protocol by the IRB and be acceptable to the Sponsor.

The patient must be provided with the patient information and informed consent form consistent with the study protocol version used and approved by the relevant IRB. The informed consent form must be in a language fully-comprehensible to the prospective patient. Patients (and/or relatives, guardians, or legal representatives, if necessary) must be given sufficient time and opportunity to inquire about the details of the study and to discuss with the Investigator and decide on their participation in the study. The patient and the person explaining about the study and with whom they discuss the informed consent will sign and date the informed consent form. A copy of the signed informed consent form will be retained by the patient and the original will be filed in the Investigator file unless otherwise agreed. The consenting process will be documented.

14.5. Study Monitoring

On behalf of the Sponsor, a clinical research organization monitor will contact and visit the Investigator at the study center as necessary before the entry of the first patient and at predetermined appropriate intervals during the study until after the last patient has completed. The clinical research organization will employ a risk-based monitoring approach that combines centralized remote monitoring and adaptive, on-site monitoring activities including source document verification to support and oversee activities being undertaken at the study center. The monitor will also perform a study closure visit.

In accordance with ICH GCP guidelines, the Investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The visits are for the purpose of verifying adherence to the study protocol and the completeness, consistency, and accuracy of data entered on the eCRF and other documents.

The Investigator will make all source data (i.e, the various study records, the eCRFs, laboratory test reports, other patient records, drug accountability forms, and other pertinent data) available for the monitor and allow access to them throughout the entire study period. Monitoring is done by comparing the relevant site records of the patients with the entries on the eCRF (i.e., source data verification). It is the monitor's responsibility to verify the adherence to the study protocol and the completeness, consistency, and accuracy of the data recorded on the eCRFs.

By agreeing to participate in the study, the Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of the monitoring visits are resolved. Contact information for the study monitor is located in the Investigator file. Representatives from the Sponsor may also contact and visit the Investigators and monitor data during the study.

14.6. 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.

14.7. Electronic Case Report Form

The data will be collected using an electronic data capture (EDC) system by remote data entry on eCRFs and by agreeing to participate in the study, the Investigator agrees to maintain accurate eCRF and source documents as part of the case history for each patient who participates in the study. Sites will receive training on the EDC system. All users will be supplied with unique login credentials.

Before study start, the Investigator will prepare a list showing the signature and handwritten initials of all individuals authorized to make or change entries on eCRFs. This "study center personnel and delegation list" must be kept current throughout the study.

For each patient enrolled, an eCRF must be completed, reviewed, signed and dated by the Principal Investigator or Co-Investigator. Data entry into the CRF should be completed within a reasonable time period after data collection, generally on the order of approximately two weeks. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

All laboratory data and Investigator observations on the results and any other clinically significant test results must be documented on eCRFs.

Full information regarding EDC and completing eCRFs is included in the Investigator files. All questions or comments related to electronic capture should be directed to the assigned monitor.

14.8. Study Termination and Site Closure

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

The Sponsor reserves the right to discontinue the study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be given.

The entire study will be stopped if:

- The protocol-specified treatment is considered too toxic to continue the study
- Evidence has emerged that, in the opinion of the Sponsor or the Investigator(s), makes the continuation of the study unnecessary or unethical
- The stated objectives of the study are achieved
- The Sponsor discontinues the development of study drug

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded on the eCRF. All reasons for discontinuation of treatment must be documented. In terminating the study, the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

14.9. Modification of the Study Protocol

Protocol amendments, except when necessary to eliminate an immediate hazard to patients, must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IRB must be informed of all amendments and give approval before their implementation. The Sponsor will submit any study protocol amendments to the concerned regulatory authorities for approval and keep the Investigator(s) updated as detailed in the ICH GCP guidelines.

14.10. Retention of Study Documents

The study site will maintain a study file, which should contain, at minimum, the IB, the protocol and any amendments, drug accountability records, correspondence with the IRB and the Sponsor, and other study-related documents.

The Investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated ICFs, copies of all eCRFs, query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the Sponsor or its designees.

The Investigator shall retain records required to be maintained for a period of 5 years after the date a marketing application in an ICH region is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until at least 5 years after the investigation is discontinued. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the Sponsor. In addition, the Investigator must make provision for the patients' medical records to be kept for the same period of time.

No data should be destroyed without the agreement of the Sponsor. Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in writing of the new responsible person and/or the new location. The Sponsor will inform the Investigator, in writing, when the study-related records are no longer needed.

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

14.11. Clinical Study Report

A clinical study report will be prepared under the responsibility and supervision of the Sponsor and signed by a Sponsor representative, thereby indicating their agreement with the analyses, results, and conclusions of the clinical study report.

14.12. Study Publication

The conditions regulating dissemination of the information derived from this study are described in the Clinical Trial Agreement.

14.13. Quality Assurance Audits

An audit visit to clinical centers may be conducted by a quality control auditor appointed by the Sponsor. The purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate study conduct and compliance with the protocol, standard operating procedures, ICH GCP and the applicable regulatory requirements. The Investigator and the Sponsor may also be subject to an inspection by the US Food and Drug Administration (FDA), Health Canada, European regulatory authorities or other applicable regulatory authorities at any time.

The auditor and regulatory authorities will require authority from the Investigator to have direct access to the patients' medical records. It is important that the Investigator(s) and their staff cooperate with the auditor or regulatory authorities during this audit or inspection.

14.14. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

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Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally-identifiable information anonymized.

Documents within Marketing Authorization Applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full clinical study reports for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target or compound class. Pfizer will make data available from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. Clinical study reports will have personally-identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to

applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

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APPENDIX A: ECOG PERFORMANCE STATUS

ECOG Performance Status	Description
0	Fully active, able to carry on all pre-disease 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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on selfcare. Totally confined to bed or chair.

APPENDIX B: RESPONSE EVALUATION CRITERIA IN SOLID TUMOR (RECIST) VERSION 1.1

The RECIST guidelines (Version 1.1) are described in Eisenhauer (2009) and at http://www.eortc.be/Recist/Default.htm. A short summary is given below.

Measurable Disease

Tumor lesions: measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with the following:

- A minimum size of 10 mm by CT scan (CT scan thickness no greater than 5 mm);
- A minimum size of 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable);
- A minimum size of 20 mm by chest X-ray.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: to be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly nomeasurable lesions, are considered nomeasurable disease. Lesions considered truly nomeasurable include leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin and lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Bone Lesions

Bone lesions, cystic lesion, and lesions previously treated with local therapy require particular comment. Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
Blastic bone lesions are nonmeasurable.

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts.
Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred as target lesions.

Lesions with Prior Local Treatment

Tumor lesions situated in a previous irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the overall tumor response.

Non-Target Lesions

RECIST criteria require unequivocal quantification of the changes in tumor size for adequate interpretation of the sum of target lesions. Consequently, when the boundaries of the primary are difficult to delineate, this tumor should not be considered a target lesion.

Guidelines for Evaluation of Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Evaluation of Target Lesions

Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable Disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Progressive Disease	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

Evaluation of Non-Target Lesions

Complete Response	Disappearance of all non-target lesions and normalization of tumor marker level.
Stable Disease/ Incomplete Response	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

If tumor markers are initially above the institutional ULN, they must normalize for a patient to be considered a complete responder.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Timepoint Response

A response assessment will occur at the protocol-specified timepoints. The tables below provide a summary of the overall response status calculation at each timepoint for patients who have measureable and non-measureable disease (non-target disease only).

Timepoint Response: Patients with Target (± Non-Target) Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; NE, Not evaluable.

Evaluation of Best Overall Response When Confirmation of CR and PR Required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

a If a CR is truly met at first timepoint, then any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, makes this disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Timepoint Response: Patients with Non-Target Lesion Assessments

Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
CR	No	CR	Normalization of tumor markers, tumor nodes < 10 mm
Non-CR/non-PD	No	Non-CR/non-PD	
Not all evaluated	No	NE	
Unequivocal PD	Any	PD	
Any	Yes	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response, which is most likely to occur in the case of PD; e.g, if only 2 of 3 baseline target lesions are assessed and result in a > 20% increase in the sum, then the patient would be assessed as a PD regardless of the missing lesion.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy) before confirming the CR status.

Confirmatory Measurement/Duration of Response

Confirmation

Radiographic tumor assessments are required. If an initial CR or PR is noted, confirmatory scans must be performed at least 4 weeks later. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of no less than 4 weeks.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).
The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Reference: Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247.

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APPENDIX D: CONTRACEPTIVE AND BARRIER GUIDANCE

- **Male Patient Reproductive Inclusion Criteria**

No contraception methods are required for male patients in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. For combination treatments in this study, consult the Doxorubicin USPI, for contraceptive method.

- **Female Patient Reproductive Inclusion Criteria**

The criteria below are part of Inclusion Criterion Number 21 (Section *Contraception*) and specify the reproductive requirements for including female patients.

A female patient is eligible to participate if she (a) is not pregnant or breastfeeding; (b) agrees to not donate eggs (ova, oocytes) for the purpose of reproduction from the time of screening through 45 days after the last dose of TTI-621 AND consult the Doxorubicin USPI; and (c) at least one of the following conditions applies:

- Is not a WOCBP

  OR

- Is a WOCBP who agrees to use a highly effective contraceptive method (failure rate of <1% per year) with low user dependency during the intervention period and for at least 45 days after the last dose of TTI-621 AND as per the relevant product label for the Doxorubicin USPI, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

  OR

- Is a WOCBP and agrees to use a highly effective (failure rate of <1% per year) user-dependent method of contraception during the intervention period and for at least 45 days after the last dose of TTI-621 (or as per the product label for the respective combination treatment), which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition to her use of the highly effective method above, she agrees to concurrently use an effective barrier method. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for reviewing the woman's medical history, menstrual history, and recent sexual activity in order to decrease the risk of enrolling a woman with an early, undetected pregnancy.

- **Woman of Childbearing and Non-Childbearing Potential**

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. **Pre-menopausal female with 1 of the following:**

   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to a medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation for any of the above categories can come from the site personnel's review of the patient's medical records, medical examination or medical history interview. The method of documentation should be recorded in the patient's medical record for the study.

2. **Post-menopausal female:**

   - A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. In addition
   - A high FSH level in the post-menopausal range must be used to confirm a post-menopausal state in women under 60 years of age and not using hormonal contraception or HRT
   - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective non-estrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of post-menopausal status before study enrollment

- **Contraception Methods**

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation
2. Intrauterine device
3. Intrauterine hormone-releasing system
4. Bilateral tubal occlusion
5. Vasectomized partner

- Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User-Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral + barrier*
    - Intravaginal + barrier*
    - Transdermal + barrier*
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral + barrier*
    - Injectable + barrier*

Sexual Abstinence

- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.

APPENDIX E: LIVER SAFETY: SUGGESTED ACTION AND FOLLOW-UP ASSESSMENTS

Potential Cases of Drug Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury but adapt are termed “adaptors.” In some patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Patients who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are “adaptors” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (i.e., AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the patient’s individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

For patients with baseline AST OR ALT OR T bili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

- Pre-existing AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller)
- Pre-existing values of T bili above the normal range: T bili level increased from baseline value by an amount of >1 × ULN or if the value reaches ≥3 × ULN (whichever is smaller)

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy’s law case should be reviewed with the sponsor.

The patient should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment.

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anti-coagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology.

A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a co-formulated product in prescription or over-the-counter medications), recreational drug or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D and E infection, liver imaging (e.g., biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

APPENDIX F: KIDNEY SAFETY: MONITORING GUIDELINES

Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and post-baseline (Scr measurement to eGFR [Scr-based eGFR]) or eCrCl.

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

Age-Specific Kidney Function Calculation Recommendations

Adults (18 Years and Above)—2021 CKD-EPI Equations

2021 CKD-EPI Scr only	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤ 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Scr-Scys Combined	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤ 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

Inker LA et al. N Engl J Med. 2021; 385:1737-49.

Adolescents (12 Years to <18 Years)—Cockcroft-Gault Formula

CrCl (mL/min)

Males: CrCl = [(140-age) × body weight (in kg)] / [Scr (in mg/dL) × 72]

Females: CrCl = 0.85 × [(140-age) x body weight (in kg)] / [Scr (in mg/dL) × 72]

Children (2 years to <12 years)—Modified Schwartz Equation

CrCl normalized to BSA (mL/min/1.73 m^2) = (K × Ht)/ Scr

Ht in cm; Scr in mg/dL.

K (proportionality constant): Female Child < 12 years: K = 0.55. Male Child < 12 years: K = 0.70

Infants (1 month to <2 years) and Neonates (<1 month)—Bedside Schwartz Equation

eGFR (mL/min/1.73 m2) = 0.413 × (Ht/Scr)

Ht in cm ; Scr in mg/dL.

Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (i.e., eGFR or eCrCl) will be according to CTCAE criteria.

APPENDIX G: PRINCIPAL INVESTIGATOR ACKNOWLEDGEMENT FORM

Protocol Title	A Phase I/II Study of TTI-621 in Combination with Doxorubicin in Patients with Unresectable or Metastatic High-Grade Leiomyosarcoma
Protocol Number	TTI-621-03
Protocol Date	17 June 2022
Protocol Version	Version 2.0
Study Drug	TTI-621 (SIRPα-IgG1 Fc)
IND Number	129118
Sponsor:	Trillium Therapeutics, a Pfizer Company. 100 Cambridgepark Drive, Suite 510 Cambridge, MA, 02140 USA

PRINCIPAL INVESTIGATOR'S ACKNOWLEDGEMENT

By signing this protocol, I confirm that I have read and agree to conduct the clinical trial as outlined in the protocol and in compliance with Good Clinical Practice, the Declaration of Helsinki as amended, and all other applicable regulatory requirements. Confidentiality of all information received or developed in connection with this protocol will be maintained by me, as well as all other personnel involved in the clinical trial who are employed by me.

The signature of the Principal Investigator below constitutes his/her agreement.

_____ _____

Print Name of Principal Investigator **Signature of Principal Investigator**

_____

Date

APPENDIX H: DOCUMENT HISTORY

Version	Date
1.0	15 April 2021
2.0	17 June 2022

Summary of changes for Version 2.0, dated 17 June 2022 provided in a separate document.