A phase II trial with a safety lead-in to evaluate the addition of APX005M, a CD40 agonistic monoclonal antibody, to standard-of-care doxorubicin for the treatment of patients with advanced sarcoma

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Background

Soft tissue sarcoma (STS) is a heterogeneous malignancy of mesenchymal origin and more than 50 subtypes are defined, each with distinct clinical and biologic features. Cytotoxic chemotherapy remains the standard approach for most STS subtypes when disease is unresectable or metastatic. Dedifferentiated liposarcoma (LPS), undifferentiated pleomorphic sarcoma (UPS), leiomyosarcoma (LMS) and synovial sarcoma (SS) represent common subtypes of STS. Doxorubicin, an anthracycline chemotherapy, represents first-line treatment for these and other STS; however, the objective response rate is approximately 15% and overall survival is limited to 16 months.

Most sarcoma subtypes are associated with copy number alterations and relatively low mutational burden, few infiltrating cytotoxic T-cells but many immunosuppressive macrophages, and absent PD-L1 expression. Studies of immune checkpoint blockade in sarcoma have shown limited efficacy outside of the UPS subtype. New immunotherapy approaches for sarcoma are needed which reflect the sarcoma immune microenvironment.

Treatment	STS Subtype	ORR	PFS
Study SARC028[1]:			
Pembrolizumab	UPS (n=40)	23%	3.0 mos
Pembrolizumab	LPS (n=40)	10%	2.0 mos
Pembrolizumab	LMS (n=10)	0%	3.7 mos
Pembrolizumab	SS (n=10)	10%	2.3 mos
Study A091401[2]:			
Ipilimumab + Nivolumab	Unselected (n=38)	16%	4.1 mos
Nivolumab	Unselected (n=38)	5%	1.7 mos

APX005M: A CD40 Agonist Antibody

CD40 is a cell surface molecule of the tumor necrosis factor (TNF) receptor superfamily and is expressed on certain immune cells - particularly antigen presenting dendritic cells, as well as B-cells, monocytes, and some tumor cells.

Effects of CD40 Ligation in the Tumor Microenvironment[3,4]
induces expression of major histocompatibility and costimulatory molecules, and TNF superfamily ligands, on APCs, particularly dendritic cells;
causes secretion of T-cell stimulatory cytokines;
functions as a key component of 'T-cell help', expanding tumor-specific T-cell clones;
reprograms tumor associated macrophages from an M2 to M1 phenotype;
is markedly more effective with chemotherapy or radiation when used in non-immunogenic, "cold", tumors.

APX005M (Apexigen, San Carlos, CA) is a humanized immunoglobulin (Ig)G1κ-agonistic monoclonal antibody which binds CD40 with high affinity and, as compared other CD40 agonists, exhibits more potent CD40-agonistic effects. In a phase 1 study, the recommended phase II dose of APX005M was 0.3 mg/kg IV once every 21 days. APX005M is currently being studied in various combinations with immunotherapy and chemotherapy. APX005M plus chemotherapy recently demonstrated promising activity in pancreatic cancer, a tumor considered non-immunogenic, similar to sarcoma[5].

APX005M represents a promising novel immunotherapy approach for sarcoma, a cancer where baseline T-cell activation is insufficient and infiltration by immunosuppressive macrophages is common. We designed a phase II study evaluating APX005M in combination with standard-of-care doxorubicin.

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(2) D'Angelo SP. *Lancet Oncol* 2018; **19**(3): 416-426.
(3) Vonderheide RH. *Clin Cancer Res* 2007; **13**(4): 1083-1088
(4) Vonderheide RH. *Cancer Immunol Immunother* 2013; **62**(5): 949-954.
(5) O'Hara MH. AACR Annual Meeting 2019; abstr CT004

Study Objectives, Design and Methodology

Primary Objective:

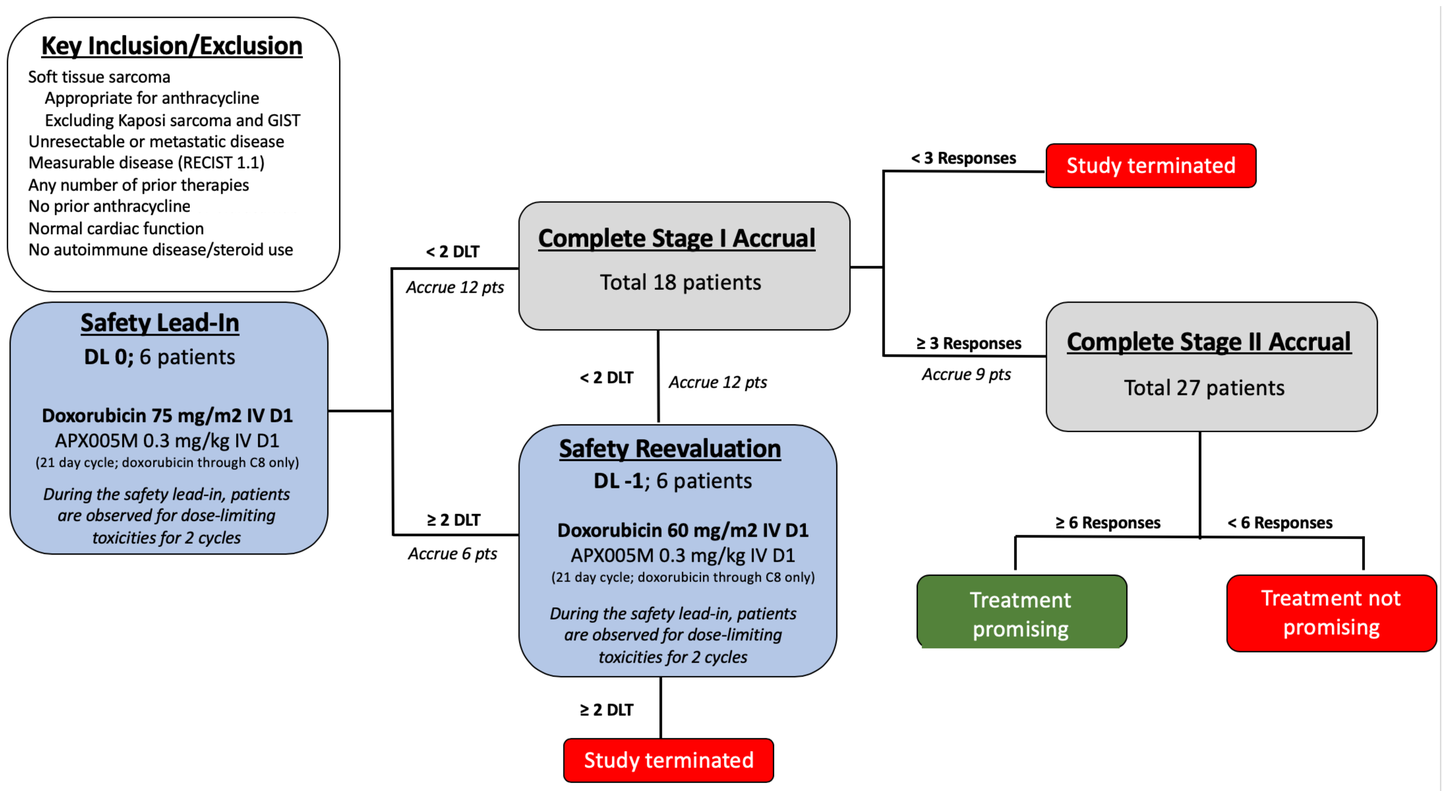
To evaluate the preliminary efficacy of combination treatment with APX005M and doxorubicin for the treatment of patients with advanced STS by evaluating for an improvement in the objective response rate from 10% (null hypothesis) to 30% (alternative hypothesis).

Secondary Objectives:

1) To confirm a safe and tolerable dose combination of APX005M and doxorubicin by performing a safety lead-in using standard dosing for doxorubicin with the RP2D of APX005M among a limited number of patients.
2) To further evaluate the efficacy of APX005M and doxorubicin by measuring progression free survival.
3) To further characterize the safety profile of APX005M and doxorubicin in the STS population.

Correlative Objectives

1) To evaluate the effects of the combination treatment on immune cells subsets in the tumor microenvironment by multiplex immunohistochemistry, gene expression profiling and related modalities using tumor tissue acquired at baseline and while on study treatment in a subset of participants.
2) To evaluate biopsy specimens from a subset of patients for tumor cell expression of CD40, and relate CD40 expression to clinical outcome from study treatment.
3) To evaluate whether composition of the gut microbiome is related to the response to study treatment by collecting stool specimens from participants at baseline and while on study treatment.



Study Design/Treatment Plan: This phase II, single-arm, open-label study employs a Simon 2-stage design to evaluate the safety and efficacy of the novel CD40 agonistic antibody APX005M in combination with standard of care doxorubicin for the treatment of advanced STS subtypes for which anthracycline chemotherapy is appropriate. Patients are treated in 21 day cycles. During cycles 1-8, patients receive doxorubicin then APX005M on day 1. For cycles 9 and after, patients receive APX005M alone on day 1. Disease status is evaluated every 2 cycles (6 weeks) by CT/MRI imaging.

Statistical Plan: We will consider an objective response rate of 10% for the doxorubicin and APX005M combination inactive and unlikely to represent an improvement over doxorubicin alone, whereas a response rate of 30% would be considered promising for further study. A Simon 2-stage design is used. The study will enroll 18 patients in the first stage. If 3 or more responses are observed, the study will accrue an additional 9 patients to complete accrual of 27 patients, otherwise the study will be closed early. If 6 or more total responses are observed among the 27 patients, the study treatment will be considered worthy of further study. This design provides for a type 1 error of 0.04 and power of 85% to detect a difference in the objective response rate between 10% and 30%.

ClinicalTrials.Gov Identifier: NCT03719430

ClinicalTrials.Gov Identifier: The study opened to accrual in 1/2019.