MSK PROTOCOL COVER SHEET

Phase II study of XmAb23104 (targeting PD-1 and ICOS), in Patients with Advanced Sarcoma

Principal Investigator/Department:
Ciara M. Kelly, MBBCh BAO,
Assistant Attending,
Sarcoma Medical Oncology Service,
Department of medicine,
Memorial Sloan Kettering Cancer Center,
300 East 66th Street,
New York, New York 10065.

Phone: 646 888 4312
Fax: 666 888 4252
Email: kellyc1@mskcc.org

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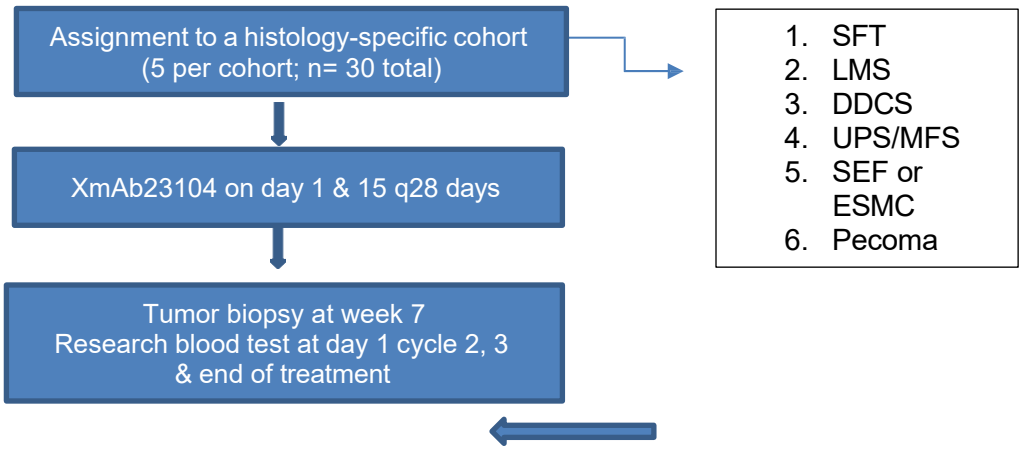
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

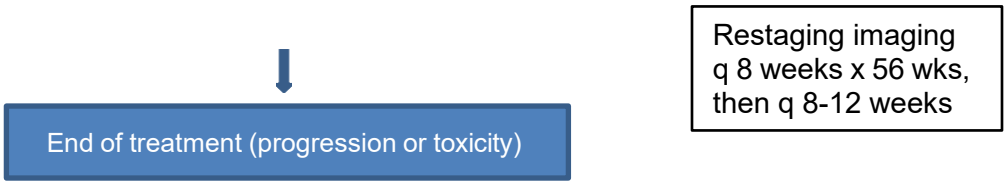
Sarcomas are a heterogenous group of mesenchymal malignancies, each with distinct pathologic features, unique molecular biology, and a varied immune microenvironment. The prognosis of unresectable or metastatic soft tissue sarcoma (STS) is poor, with a median overall survival (OS) of less than two years. Chemotherapy remains the standard of care first-line treatment for patients with advanced STS, providing a progression-free survival (PFS) of approximately 6 months. There is an unmet medical need for novel treatment approaches in patients with metastatic high-grade STS. Translational and clinical studies have documented that patients with certain high-grade STS subtypes, including undifferentiated pleomorphic sarcoma (UPS), myxofibrosarcoma (MFS), dedifferentiated liposarcoma (LPS), leiomyosarcoma (LMS), and angiosarcoma (AS), can respond to immune checkpoint blockade (ICB), although many patients remain refractory to PD- 1 or PD-L1 blockade.

This phase II, open-label, single-center study will investigate the safety and efficacy of XmAb23104, an anti-PD-1 and ICOS antibody in patients with locally advanced or metastatic sarcoma. Patients on this study will receive treatment with XmAb23104 on day 1 and 15 of each 28-day cycle for up to 24 months depending on response and tolerability.

In this phase II study, patients will be stratified into one of six cohorts based on sarcoma histologic subtypes to receive treatment: 1) Malignant solitary fibrous tumor (SFT), 2) Leiomyosarcoma (LMS), 3) Dedifferentiated chondrosarcoma (DDCS), 4) Undifferentiated pleomorphic sarcoma (UPS) or myxofibrosarcoma (MFS) 5) Translocation associated sarcoma: Sclerosing epithelioid fibrosarcoma (SEF) or Extraskeletal myxoid chondrosarcoma (ESMC), 6) Pecoma. Patients with UPS will be eligible if they have refractory to or relapsed after anti-PD-(L)1 therapy and demonstrated clinical benefit to immunecheckpoint inhibition [complete/partial response or stable disease >/=6 months]) Treatment with XmAb23104 will be continued until progression of disease, unacceptable toxicity, or completion of 24 months of study therapy. The primary objective of this phase II study is to determine the proportion of patients who achieve partial response and complete response at 24 weeks. To assess the potential effect of XmAb23104 on selected biomarker expression, all patients will undergo mandatory research biopsies after 7 weeks for characterization of PD-1/PD-L1/ICOS expression, TILs, gene expression profiling, and characterization of T-cell receptor clonality in TILs (Figure 1).

Figure 1: Study flowchart





2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objective

To evaluate the efficacy, as assessed by best objective response rate (partial response [PR] and complete response [CR]) at 24 weeks, as defined by RECIST v1.1, of XmAb23104 in patients with advanced sarcoma.

2.2 Secondary Objectives

1. To evaluate the safety and tolerability of XmAb23104 in patients with advanced sarcoma.
2. To evaluate the efficacy, as assessed by the clinical benefit rate (stable disease [SD] for ≥ 16 weeks + PR at 48 weeks + CR at 48 weeks), as defined by RECIST v1.1, of XmAb23104 in patients with advanced sarcoma.
3. To assess the progression free survival (PFS) rate at 6 months, overall survival (OS) at 12 months, median PFS, and median OS for patients treated with XmAb23104 in patients with advanced sarcoma.
4. To assess the duration of response, as defined by RECIST v 1.1 of XmAb23104 in patients with advanced sarcoma.

2.3 Exploratory Objectives

1. To determine the baseline characteristics of sarcoma tumors (pre-treatment biopsy sample) evaluated in this study including level of PD-1/PD-L1/ICOS expression, presence of tumor infiltrating lymphocytes (TILs) and tumor antigens, gene expression profile and T-cell receptor clonality in TILs.

2. To assess the potential effect of XmAb23104 on selected biomarker expression measured in post-treatment tumor tissue and the association between these biomarkers (baseline level of expression and the change in biomarker level of expression following treatment) and clinical outcome, including characterization of PD-1/PD-L1/ICOS expression, TILs, gene expression profiling, and characterization of T-cell receptor clonality in TILs.

3. To evaluate the associations between selected biomarkers measured in serial peripheral blood and clinical efficacy, including immunophenotyping and functional analyses, evaluation of serum levels of chemokines, cytokines and other immune mediators, and characterization of T-cell receptor clonality in peripheral blood.

3.0 BACKGROUND AND RATIONALE

Sarcomas: New therapies are desperately needed

Sarcomas are heterogeneous malignant tumors of mesenchymal origin characterized by more than 80 distinct subtypes. Approximately 13,000 cases of soft tissue and bone sarcomas are diagnosed annually in the US. Despite primary combined modality therapy, between 25-50% of patients develop recurrent and/or metastatic disease. Complete responses (CR) to chemotherapy for recurrent or metastatic sarcoma are rare, and the median survival in the metastatic setting is approximately 15-18 months. Standard cytotoxic chemotherapy agents such as doxorubicin, gemcitabine/docetaxel, and dacarbazine have response rates of 10-20%. The development of novel and effective therapies is desperately needed for patients with sarcomas.

Immune Checkpoint Inhibition in sarcoma

A limited number of immunotherapy sarcoma specific trials have been completed to date. The SARC028, phase II study examined pembrolizumab monotherapy in patients with advanced sarcoma. Clinical activity was observed in undifferentiated pleormorphic sarcoma (UPS) and dedifferentiated liposarcoma (DDLPS).[6] The histology specific expansion cohorts in this study demonstrated responses in 9 (23%) of 40 patients with UPS, two of which were CRs (by RECIST v1.1) and in 4 (10%) of 39 patients with DDLPS.[7] The Alliance (A091401) phase II, non-comparative study, led by Sandra D'Angelo at MSKCC, randomized 80 patients to receive nivolumab alone or in combination with ipilimumab. The objective response rate was 16% in the combination arm while that in the monotherapy arm was 3%. Responses were again observed in UPS but clincal activity was also seen in other sarcoma subtypes such as angiosarcoma, leoimyosarcoma and myxofibrosarcoma.[8] Results of the expansion phase of this study reported an objective response rate of 27% in the combination arm of the UPS cohort. UPS represents a genomically complex sarcoma with a higher mutational burden, a relatively high T-cell fraction and high levels of PD-1 and PD-L1 expression.[9]
PD-L1 expression in association with immune-infiltrating cells and HLA class I expression was consistently identified in nearly 50% of patients with dedifferentiated chondrosarcomas which provides strong rationale for including these patients in clinical trials incorporating immune checkpoint inhibition.[30] An objective response rate of 54% was observed in patients with advanced alveolar soft part sarcoma receiving pembrolizumab in combination with axitinib while atezolizumab monotherapy demonstrated an objective response rate of 42% in this sarcoma subtype.[32, 33] Sclerosing epithelioid fibrosarcoma is an aggressive variant of fibrosarcoma characterized by the EWSR1-CREB3L1/2 gene fusion. Standard chemotherapy options used to treat advanced sarcoma have limited activity in this subtype. Reports of response to immune checkpoint blockade in this subtype were recently published.[34, 35] In a case series of patients with advanced SEF demonstrating response to immune checkpoint blockade both cases reported had evidence of relatively high frequencies of infiltrating CD8+ T-cells and tumor cell PD-L1

expression.[35] Perivascular epithelioid cell tumors, otherwise known as Pecomas, are mesenchymal neoplasms composed of histologically and immunohistochemically distinctive epithelioid or spindle cells, which are immunoreactive for both smooth muscle and melanocytic markers. Pecomas constitute a genetically diverse group that includes neoplasms harboring TFE3 gene rearrangements and more commonly those with TSC2 mutations leading to elevated mechanistic/mammalian target of rapamycin complex activity. Preclinical studies have shown that programmed death 1 co-inhibitory receptor (PD-1) is upregulated on T cells in TSC associated tumors and that anti-PD1 therapy in a TSC2 deficient mouse model resulted in a 67% decrease in tumor growth ($p<0.0001$).[36]
A phase II study evaluating durvalumab (anti- PD- L1) and tremelimumab (anti- CTLA- 4) resulted in objective responses in 5 (50%) of 10 patients with alveolar soft part sarcoma (ASPS).[10] While limited by small numbers, these results highlight the potential importance of combinatorial immunotherapy strategies and sarcoma subtype selection for the future design of immunotherapy trials for sarcoma. To improve on clinical efficacy, there has been significant interest in combining checkpoint blockade antibodies with other systemic approaches such as chemotherapy, targeted therapy, radiation therapy and other immunotherapeutics which have been shown to stimulate immune cells, including CD4+ and CD8+ T cells,[11, 12] natural killers cells,[13] and dendritic cells.[14]
Solitary fibrous tumor (SFT) comprises a histologic spectrum of rarely metastasizing fibroblastic mesenchymal neoplasms characterized by a gene fusion involving NAB2-STAT6. Advanced SFT are challenging to treat with limited effect therapeutic options available. Treatments that have demonstrated some activity in this disease include tyrosine kinase inhibitors, temodar and bevacizumab. Immunotherapy has not been widely explored in this subtype to date. However, there are anecdotal reports of activity with immunecheckpoint inhibition in this disease.[44]

Combination Immunotherapy Approaches Targeting Different Aspects of the Immune Activation Cascade

Responses to anti-PD-1 monotherapy rely primarily on the presence of pre-existing T-cell infiltrate that is inhibited by PD-1:PD-L1 interactions. Higher objective response rates have been observed when anti-PD-1 therapy has been combined with additional immune modulation aiming to recruit new antigen-specific T-cells into tumors. The power of a combination immunotherapy strategy in sarcoma, is reflected in the results of the Alliance A091401 previously discussed and a phase II study of the intra-tumoral injection of talimogene laherparepvec (T-VEC) in combination with pembrolizumab in patients with advanced sarcoma, led by Dr. Kelly. T-VEC and pembrolizumab modulate the immune system in complementary ways. T-VEC is an oncolytic immunotherapy designed to self-replicate within tumor cells, which subsequently causes their lysis, thereby increasing tumor-specific immune activation via the augmentation of antigen presentation and T-cell priming. Concurrently, pembrolizumab negates the downregulation of effector T-cell activity within peripheral tissue and tumors. The objective response rate observed in this study was 35%, one of the highest reported in a sarcoma-specific immunotherapy trial to date.[15] These results have excited interest to explore novel combination immunotherapy strategies in sarcoma. Although a subset of sarcoma appears inflamed and responsive to immune checkpoint blockade with PD-1 targeted agents, novel immunotherapies and combinations likely will be needed for most subtypes. A variety of approaches—including targeting immune checkpoints other than PD-1 such as B7-H3, OX40, GITR, and ICOS; modulating tumor associated macrophage phenotype from tumor-promoting to tumor- suppressive status; using cellular based therapies, such as chimeric antigen and high-affinity T-cell receptors to deepen the adaptive immune response; and reinvigorating older approaches, such as vaccines and oncolytic virus-based treatments all merit exploration in sarcomas.[16]

ICOS-ICOS ligand costimulatory pathway in cancer immunotherapy

The inducible costimulator (ICOS or cluster of differentiation (CD278)) of T cells and its ligand (ICOSL) play important roles in memory and effector T cell development and specific humoral immune responses. ICOS is inducible and expressed following T-cell activation.[17] This pathway has been shown to exert opposing effects on the various T cell subpopulations. Interactions between ICOS and ICOSL can potentiate immunosuppression mediated by some CD4+ T cell subsets, such as regulatory T cells (Tregs). This pathway can also promote anti-tumor T-cell effects when activated in Th1 and other Teff cells.[18] This dual role in both anti-tumor and pro-tumor activities makes targeting the ICOS/ICOSL pathway attractive for enhancement of anti-tumor immune responses. Thus, a potential role for this pathway in improving the effectiveness of cancer immunotherapy is being investigated in early phase trials using agonistic or antagonistic antibodies administered alone or more often in combination with other immunotherapeutic treatments.

ICOS targeted agents alone or in combination with anti-PD1 blockade and/or anti-CTLA4 blockade

In preclinical studies, ICOS agonistic monoclonal antibodies (mAbs) can potentiate the effects of anti-CTLA-4 therapy. In preclinical studies ICOS knockout mice responded poorly to anti-CTLA4 therapy which suggests that ICOS signaling is a crucial player in how CTLA4 blockade exerts anti-tumor effects.[19] Treatment with ipilimumab has also been shown to increase the frequency of ICOS+ Th1-like CD4 effector cells in the tumor.[20-22] In another study, a gene expression profile that included ICOS demonstrated that ICOS expression was associated with greater survival in metastatic melanoma patients.[23] The combination of CTLA4 blockade and ICOS stimulation in melanoma and prostate mouse models demonstrated superior anti-tumor effects compared to anti-CTLA4 therapy alone.[24]
PD-L1 blockade in tumor mouse models induced selectively the expansion of tumor-infiltrating CD4+ and CD8+ T-cell subsets, co-expressing both activating (ICOS) and inhibitory (LAG-3, PD-1) molecules (T_{AI} cells). By therapeutically co-targeting these molecules on the T_{AI} cell subsets in vivo by agonistic and antagonist antibodies, led to enhanced efficacy of PD-L1 blockade therapy as evidenced by an increased number of T_{AI} cells within the tumor micro-environment and improved tumor protection.[25]

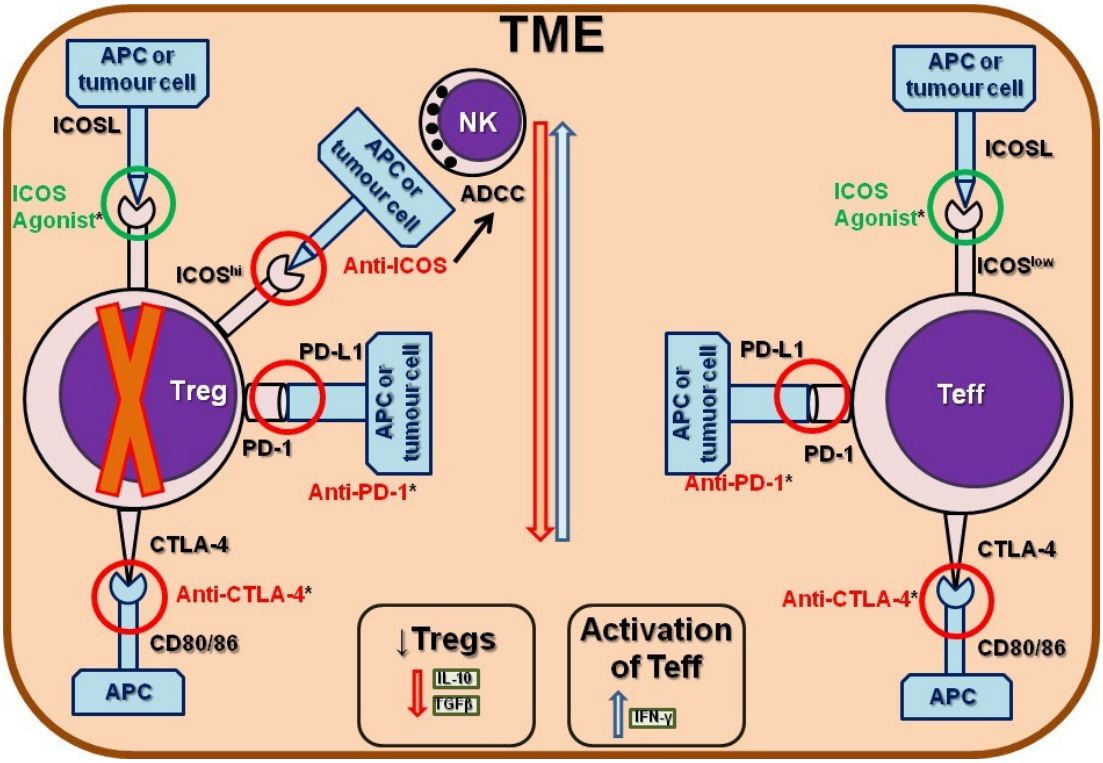


Figure 3. Targeting regulatory and/or effector T cells with ICOS agonistic or antagonistic antibodies. ICOS can be targeted by either agonist (in green) and antagonistic (in red) antibodies (Abs). ICOS agonists are usually administered in concomitance with anti-CTLA-4 or anti-PD-1 Abs, for their ability to synergistically inhibit the suppressive activity of regulatory T cells (Tregs) and to potentiate the anti-tumour activity of effector T cells (Teff), including CD4+ and CD8+ subpopulations. One main mechanism of action of ICOS antagonistic Abs is to inhibit Tregs by stimulating the antibody-dependent cell-mediated cytotoxicity (ADCC) mediated by natural killer (NK) cells. CTLA-4, cytotoxic T-lymphocyte Ag-4; PD-1, programmed celldeath-1.

Early phase clinical trials testing ICOS agonist Abs in patients with advanced solid tumors have shown good safety profiles and promising anti-tumor activities, particularly when the compounds are given in combination with anti-PD-1 agents (pembrolizumab and nivolumab). Dose-limiting toxicities were not common occurrences, reinforcing these agents as promising new targets for combination cancer immunotherapy. The first-in-human trial, INDUCE-1 (NCT02723955), used an ICOS agonist Ab administered alone (part 1) or in combination with an anti-PD-1 antibody (pembrolizumab; part 2) in patients with advanced solid tumors and had promising results in terms of tolerability, toxicity profile and clinical activity.[26] The ICONIC trial (NCT02904226) investigated the role of an ICOS agonist Ab (JTX-2011) given alone (mono arm) or in combination with an anti-PD-1 antibody (nivolumab; combo arm) in patients with relapsed/refractory tumors.[27] Currently, the data shows this compound is safe, well tolerated and can generate anti-tumor responses in heavily pretreated gastric cancer and triple-negative breast cancer patients. Interestingly, peripheral blood CD4+ICOShi T cell subpopulations appear to be a promising biomarker of response.[28]

ICOS expression in sarcoma

Dufresne et al, recently examined the gene expression profiles of 93 immune checkpoint (ICP) membrane markers of immune cells in a series of 253 soft tissue sarcoma (synovial sarcoma, myxoid

liposarcoma, sarcoma with complex genomic signatures and gastrointestinal stromal tumors [GIST]) using Agilent Whole Human Genome Microarrays. Unsupervised hierarchical clustering of gene expression level was found to properly categorize patients according to their histological subgroup of sarcoma, indicating that each sarcoma subgroup is associated with a specific immune signature defined by its gene expression pattern. In general, synovial sarcoma had a consistently low level of expression for all ICPs conversely, the highest expression was in general reported for GIST and sarcomas with complex genomic signatures. The differential expression of each gene across sarcoma subgroups is highlighted in figure 4. The highest level of ICOS and PDCD1 expression was observed in sarcomas with complex genomic signatures which included UPS (n=30), LMS (n=24), DDLPS (n=11), MFS (n=7), pleomorphic LPS (n=6), and adult fibrosarcomas (n=3).[29]

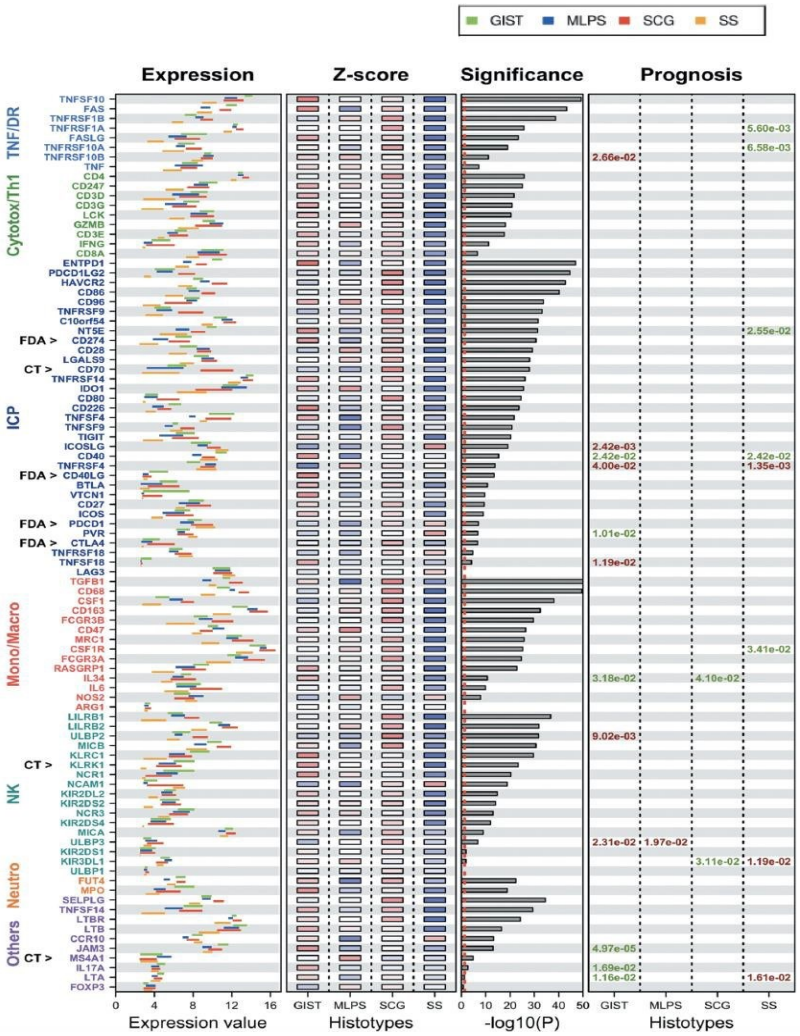


Figure 4. Expression level of the 93 ICP/MM genes across each sarcoma subtype.
The gene expression value is displayed by bars representing the 25 and 75 percentile of expression level for each ICP/MM. Each sarcoma subtype is shown (green: GIST; blue: MLPS; red: SCG; orange: SS)- The Z-score is averaged for each gene within each sarcoma subgroup (red corresponding to the highest expression and blue the lowest one; from 2 to −2, respectively)- The significance displays the relationship between expression values across histological subtype given by multiple Bonferroni-adjusted ANOVA, ranked from high significance (top) to non-significant (bottom). Vertical dashed line indicates significance threshold (p = .05), 84 genes out of 93 (90%)

are differentially expressed in the different subtypes- The prognosis represents the impact of an ICP/MM gene expression on MFS. A positive prognostic impact (high expression correlated with longer MFS) and is represented in green. A negative impact (high expression correlated with shorter MFS) and is represented in red.- CT and FDA highlight genes whose protein is targeted in a Clinical Trial or by a Food and Drug Administration approved agent.

XmAb23104: Simultaneous targeting of PD-1 and ICOS

XmAb23104 is a humanized bispecific monoclonal antibody manufactured by Xencor that binds the immune checkpoint molecule PD1 and the costimulatory molecule ICOS. While XmAb23104 is expected to preferentially bind cells that simultaneously express ICOS and PD1, the anti-ICOS arm is believed to have immune agonist activity. Acting together, PD1 relieves exhausted T cells in the tumor microenvironment (TME), and ICOS costimulates T cells to enhance immune activation. Consistent with its intended mechanism of action and functional properties, XmAb23104 has been shown to interfere with binding of PDL1, PDL2 and ICOSL with PD1 and ICOS in a dose-dependent fashion. This was demonstrated by in vitro assays that involved treatment of HEK293T cells, which overexpress PD1 and ICOS, with increasing doses of XmAb23104, followed by flow cytometry to assess the inhibition of binding of soluble PDL1, PDL2, and ICOSL. Furthermore, XmAb23104 dose dependently promoted IL-2 and IFNγ release following stimulation of peripheral blood mononuclear cells (PBMC) with super-antigen Staphylococcal enterotoxin B (SEB). The mean EC_{10}, EC_{20}, EC_{30}, EC_{50}, EC_{80}, and EC_{90} for XmAb23104-induced IL-2 release from SEB-stimulated human T cells was 44, 79, 125, 279, 1201, and 3215 ng/mL, respectively. The mean EC_{10}, EC_{20}, EC_{30}, EC_{50}, EC_{80}, and EC_{90} for XmAb23104-induced IFN-γ release from SEB-stimulated human T cells was 21, 34, 48, 81, 206, and 384 ng/mL, respectively. The same response was also demonstrated in SEB-stimulated cynomolgus monkey PBMCs. When incubated with human PBMCs, XmAb23104 did not induce cytokine (IFN-γ, TNF-α) or interleukin (IL-2, IL-4, IL-6, or IL-10) production.

As of 03 November 2020, 46 subjects have been treated with XmAb23104 at dosages between 0.002 and 10 mg/kg. At the 0.2 mg/kg dose level, 1 subject has received 24 doses, including one intra-subject dose escalation at Cycle 7, Day 15.
The most common treatment-related treatment-emergent adverse event (TEAE) has been fatigue, observed in 10 subjects. In addition, 5 subjects experienced immunotherapy-related AEs (IRAEs) and 1 subject experienced an infusion-related reaction (IRR).
The mean half-life of XmAb23104 is approximately 9 days. Insufficient data are available at this time to accurately define efficacy and PD.

Hypothesis and Rationale

Based on the preclinical data, we hypothesize that combined anti-PD-1 and anti- ICOS therapy in advanced sarcoma with specific histological subtypes including LMS, DDLPS, dedifferentiated chondrosarcoma, ASPS, SEF and pecoma, will result in synergistic anti-tumor activity.

The importance of ICOS engagement is supported by the superior activity of 5 mg/kg XmAb23104 (a dose with equivalent molar quantity of PD1 binding arms to that of the 3 mg/kg anti-PD1 dose) which significantly suppressed tumor growth in huPBMC engrafted mice in comparison to anti-PD1 (XENP16432). Also, treatment with 0.3 mg/kg and 1.0 mg/kg XmAb23104 (doses with a lower molar quantity of PD1 compared to the 3.0 mg/kg anti-PD1) displayed anti-tumor activity that was comparable to that of anti-PD1 (XENP16432).

The impact of varying concentrations of nivolumab or pembrolizumab was also studied on the binding of XmAb23104 to PD1+ICOS+ cells. Monospecific anti-PD1 antibodies nivolumab and pembrolizumab are FDA approved for several oncology indications, and many subjects who are among the target populations for the XmAb23104 clinical trials may have received one of these agents immediately before enrolling in an XmAb23104 clinical trial. Given the relatively long half-lives of these antibodies, these subjects may continue to have detectable serum concentrations of nivolumab or pembrolizumab for a period of time after dosing has ceased. When the impact of pembrolizumab or nivolumab on the binding of XmAb23104 to PD1+ICOS+ HEK293T cells was estimated, pembrolizumab interfered with XmAb23104 binding in a dose-dependent manner. In contrast, nivolumab competed much less effectively with XmAb23104 for cell binding. Pembrolizumab has a terminal elimination half-life ($t_{1/2}$) of 22 days and a median steady state, maximum observed serum concentration (C_{max}) and trough concentrations of 66.3 µg/mL and 27.6 µg/mL, respectively, when administered at a dose of 200 mg every 3 weeks. Some of the subjects who are eligible for this clinical trial of XmAb23104 may have been recently treated with approved anti-PD1 mAbs including pembrolizumab. Therefore, patients who have received pembrolizumab within 6 weeks of enrollment will not be eligible for this study.

Identifying Predictive Biomarkers of Response to ICB

Ultimately, the major challenge to harnessing immune checkpoint inhibitors in sarcomas is identifying patients who have the highest chance of benefit. To do this, lessons can be learned from other tumor types and applied to sarcomas. We believe the heterogeneity inherent in sarcomas can make them an ideal tumor type to validate a prospective biomarker for response to immune activating agents. It is unclear how best to predict which patients will benefit from ICB. While the initial phase I trial of nivolumab suggested tumors expressing PD-L1 by immunohistochemistry (IHC) may benefit more frequently from PD-1 blockade,[35] more recent data from the combination ipilimumab plus nivolumab trial has cast doubt on the theory that PD-L1 expression is necessary for therapeutic benefit. Among patients that received combination therapy, responses were seen both in patients with PD-L1 expression (6/13) or those without PD-L1 expression (9/22.) It is known that PD-L1 expression remains a dynamic marker that can change over time and under different conditions in the microenvironment. Tumor heterogeneity can also contribute varied PD-L1 expression.[36] These data suggest either PD-L1 expression may change as a result of therapy with immune checkpoint inhibitors or that other mechanisms underlie the response to immune checkpoint blockade.

The Angiosarcoma project, a patient-partnered research initiative that obtained whole exome sequencing on 47 angiosarcoma tumors with matched normal tissue identified that angiosarcomas of the head, neck, face, and scalp (HNFS) were associated with a high tumor mutation burden (median 20.7 mutations/Mb compared to 2.8 mutations/Mb in the remainder of the cohort) and a dominant ultraviolet damage mutational signature in 10 of 12 cases (COSMIC Signature 7). They report that 3 patients with angiosarcoma of the HNFS received immune checkpoint blockade; 2 of whom experienced dramatic responses to immunotherapy after progressing on standard of care treatment.[37] This suggests that a high TMB and a UV signature may be two biomarkers predictive of response to checkpoint blockade in sarcoma.

In an in-depth analysis of 52 undifferentiated high-grade sarcomas with whole-genome sequencing, Steele et al[38] reported that in contrast to the majority of undifferentiated sarcomas with low TMB, a subgroup of these tumors (13%; n = 7) has a high TMB and low copy number alteration burden. 5 of these patients had an oncogenic mutation, copy-number loss, or promoter methylation of a Lynch

syndrome-associated gene either in the tumor or the germline associated with genomic signatures of mismatch repair deficiency. The other patient had a mutational signature (signature 30) strongly matching the base excision repair *NTHL1* deficiency pattern, which was associated with a germline *NTHL1* mutation and loss-of- heterozygosity of the wild type allele. The final patient with a high TMB had genomic signature 1, likely caused by spontaneous deamination of methylated cytosines and biallelic inactivation of the DNA glycosylase gene *MBD4*, which is a binding partner of the MMR protein MLH1. The better prognosis compared to the mutation-low sarcomas. Pathway analysis revealed significant enrichment for immune-related pathways in the mutation high compared with other samples. This analysis also highlights the importance of identifying specific genomic signatures in sarcoma as well as overall tumor mutation burden to predict potential immunogenicity of undifferentiated sarcomas.

Recent studies have investigated the tumor microenvironment across a range of STS subtypes using publicly available gene expression profiles. Five distinct sarcoma immune classes (SICs) were proposed: immune desert (SIC A), vascularized (SIC C; high expression of endothelial-cell related genes), immune and tertiary lymphoid structure (TLS) high (SIC E), heterogenous but generally immune-low (SIC B), or heterogenous but generally immune high (SIC D). SIC E is characterized by the highest expression of genes specific to immune populations, such as T cells, CD8+ T cells, NK cells, and cytotoxic lymphocytes. SIC E were also high in the expression of the lymphoid-structures-associated B-cell-specific chemokine CXCL12, whereas PD-L1 was heterogeneously expressed across SICs. SICs D and E had high expression of genes associated with T cell or myeloid cell chemotaxis, T cell activation and survival, MHC class I, regulatory gene signatures, as well as immune-checkpoint-related genes. Patients with SIC D or E had the highest overall survival among 496 patients with survival data available. When survival was stratified by the dominant immune cell type, the B lineage signature was associated with survival on a multivariable analysis.[39]

Using the SIC classification, 47 patients treated with pembrolizumab were analyzed both before and after treatment to determine the association between SIC and outcome. SIC E patients (DDLPS and UPS patients) had the highest overall response rate (50%; 5 of 10), followed by SIC D (DDLPS and UPS; 25%; 3 of 12) and SIC C (Synovial sarcoma, LMS, UPS and DDLPS; 22%; 2 of 9). There were no responders in SIC A or B (5 and 11 patients, respectively), which included DDLPS, synovial sarcoma, LMS, and UPS patients.[39] Thus, stratification of patients by sarcoma immune class could accurately predict response to immune checkpoint blockade and the presence of tertiary lymphoid structures was associated with response.

This trial will obtain pre- and on-treatment biospecimens to further explore predictors of response to XmAb23104 including tumor biopsies and peripheral blood. Aside from PD-L1 and ICOSL expression in tumor and infiltrating immune cells, unique gene expression profiles can potentially be utilized to predict responses to treatment. Additionally, utilizing deep sequencing with the targeted gene panel on MSK-IMPACT we will attempt to correlate specific genomic alterations, as well as TMB, and microsatellite instability status with clinical outcome to therapy on this study.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

The study is an open-label, single institution phase II trial of XmAb23104 in patients with locally

advanced or metastatic sarcoma. Patients will receive the recommended phase II dose of XmAb23104 monotherapy on day 1 and 15 of each 28-day cycle. Patients will continue XmAb23104 (day 1 & 15, q 28 days) for up to 24 months depending on their response and tolerability to treatment. Treatment will be continued until progressive disease (PD) or toxicity or a total of 24 months of study therapy has been completed.

4.2 Intervention

Thirty patients will be enrolled in this study. Patients will be stratified based on sarcoma histological subtype into one of 6 cohorts with 5 patients per cohort including SFT, LMS, DDCS, UPS/MFS, SEF or ESMC, and pecoma. Study involves XmAb23104 monotherapy. The cycle will be 28 days at length. Participants will be given the recommended phase II dose of XmAb23104 (10 mg/kg) intravenously on days 1 and 15 of each 28-day cycle. XmAb23104 will be administered by IV infusion at a constant rate over 1 hour. The treatment with XmAb23104 will continue until unacceptable toxicity, disease progression, or the completion of 24 months. Physical examinations and pre-dose clinical evaluations may be performed up to 24 hours prior to a scheduled infusion of XmAb23104. Radiographic assessment by RECIST v1.1 will occur at baseline, after the first two treatment cycles, and every 8 weeks for the first 56 weeks of study treatment, followed by every 8-12 weeks thereafter at the discretion of the treating investigator. Mandatory tumor biopsies will be performed at baseline and week 7.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

5.1 XmAb23104

5.1.1 Availability

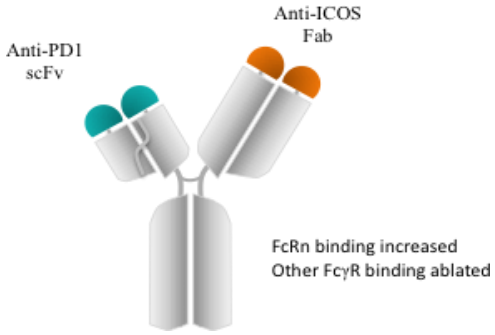
Xencor will provide investigational supply of XmAb23104 to patients enrolled on this protocol free of charge for the duration of the study. A complete description of the drug, its clinical pharmacology, contraindications and adverse reactions are available in the investigator's brochure. MSK will be cross-referencing Xencor's IND for XmAb23104.

5.1.2 Mechanism of Action

XmAb23104 is a humanized bispecific antibody that binds the immune checkpoint molecule PD1 and the costimulatory molecule ICOS. XmAb23104 is expected to preferentially bind cells that simultaneously express ICOS and PD1. To generate XmAb23104, Xencor humanized, and affinity-optimized anti-PD1 and anti-ICOS antibodies and combined them in a single bispecific molecule. XmAb23104 is produced as a 3-chain scFv-Fab-Fc antibody (Figure 5), in which the single-chain Fv (scFv) domain targets PD1 and the antigen-binding fragment of an antibody (Fab) domain targets ICOS. XmAb23104 has an Fc region that has been engineered to remove binding to Fc gamma receptors (FcγRs), with the intent of preventing activation and/or depletion of T cells via engagement of

XmAb23104 by FcγR-expressing cells. The FcRn affinity has been increased via amino acid engineering to improve serum half-life relative to antibodies containing native IgG Fc domains.

Figure 5: Schematic of XmAb23104 PD1 × ICOS Bispecific Monoclonal Antibody



Fab = fragment, antigen binding; Fc = fragment, crystallizable; FcγR = Fc gamma receptor; FcRn = Fc neonatal receptor; scFv = single-chain variable fragment (immunoglobulin fusion protein).

5.1.3 Formulation and Storage

XmAb23104 is a sterile liquid product supplied in single-use glass vials filled with 10.0 mL at a concentration of 10.0 mg/mL in 20 mM acetate, 250 mM sorbitol at pH 5.5. It should be stored under refrigeration at 2°C to 8°C, protected from light.

5.1.4 Administration

XmAb23104 is administered in a dose of 10mg/kg over 60 minutes (+15 minutes) every 2 weeks. The full calculated dose should be administered based on the patient's actual baseline weight measurement in kilograms. Following the first dose, subsequent doses will only be modified if the patient's weight changes by more than 10% from the baseline weight, at which point it will be recalculated using the current weight. See the pharmacy manual for specific dosing information.

XmAb23104 should be infused through a dedicated peripheral IV (PIV)

XmAb23104 may be infused through central lines, including PICCs, PORTs and mid-lines.

The drug should be infused over 1 hour. For patients >120 kg, bag 1 and bag 2 would each be infused

over 30 minutes for a total of 1 hour.

6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY

6.1 Participant Inclusion Criteria

- Male or female age ≥ 18 years at the time of informed consent
- Be capable, willing, and able to provide written informed consent/assent
- Be willing to comply with clinical trial instructions and requirements, including mandatory biopsies at baseline and on-treatment where feasible
- Patients must have progressed on or be intolerant of at least one prior standard systemic therapy where available. If a patient declines standard systemic therapy they will be considered eligible.
- Patients must have a histologically confirmed locally advanced/metastatic sarcoma with select histological subtypes including:
    - i) malignant solitary fibrous tumor (SFT)
    - ii) leiomyosarcoma (LMS)
    - iii) dedifferentiated chondrosarcoma
    - iv) undifferentiated pleomorphic sarcoa/myxofibrosarcoma (Patients with UPS/MFS will be eligible if they have refractory to or relapsed after anti-PD-(L)1 therapy and demonstrated clinical benefit to immunecheckpoint inhibition [complete/partial response or stable disease >/=6 months])
    - v) sclerosing epithelioid fibrosarcoma (SEF) or extraskeletal myxoid chondrosarcoma (ESMC)
    - vi) pecoma.
- Adequate performance status: ECOG 0 or 1/KPS 100-70%
- Expected life expectancy >3 months
- Presence of measurable disease per RECIST v1.1.
    - Target lesion(s) 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.
- Adequate organ function determined within 10 days of treatment initiation
    - Platelet count > 100 x 10^9/L
    - Hemoglobin level > 8.0 g/dL
    - Absolute neutrophil count > 1.0 x 10^9/L
    - AST at screening < 3 x ULN for subjects without known liver involvement by tumor; or < 5 x ULN for subjects with known liver involvement by tumor
    - ALT at screening < 3 x ULN for subjects without known liver involvement by tumor; or < 5 x ULN for subjects with known liver involvement by tumor
    - Bilirubin ≤ 1.5 × ULN (unless prior diagnosis and documentation of ongoing hemolysis or Gilbert's syndrome has been made)
    - Estimated creatinine clearance (CL) > 30 mL/min calculated by the Cockcroft-Gault or modification of diet in renal disease formulas
- Male subjects must agree to use contraception and refrain from donating sperm during the treatment period and for at least 8 weeks after the last dose of XmAb23104
- Female subjects of childbearing potential must agree to use a highly effective method of birth control during and for 8 weeks after completion of study. Women are considered to be of childbearing potential unless it is documented that they are over the age of 60 OR postmenopausal by history

with no menses for 1 year and confirmed by FSH OR have a history of hysterectomy and/or bilateral oophorectomy OR have a history of bilateral tubal ligation. Highly effective methods of birth control include hormonal birth control (oral, intravaginal, transdermal, implantable, or intrauterine device [IUD]), IUDs (non-hormonal), vasectomy (in male partner), or any double-barrier methods (combination of male condom and spermicide with either cap, diaphragm, or sponge).

6.2 Participant Exclusion Criteria

- History of unstable or deteriorating cardiovascular disease within the previous 6 months prior to screening including but not limited to the following:
  - Unstable angina or myocardial infarction
  - CVA/stroke
  - Congestive heart failure (New York Heart Association [NYHA] Class III or IV
  - Uncontrolled clinically significant arrhythmias
- Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases or carcinomatous meningitis 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 on imaging performed during study screening, and are not using steroids for at least 14 days prior to trial treatment
- Current use of immunosuppressive medication, EXCEPT for the following:
  - intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection)
  - Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent
  - Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

- Evidence of clinically significant immunosuppression such as the following:
  - Primary immunodeficiency state such as Severe Combined Immunodeficiency Disease
  - Concurrent opportunistic infection
  - Receiving systemic immunosuppressive therapy (> 2 weeks) including oral steroid doses > 10 mg/day of prednisone or equivalent within 2 months prior to enrollment

- History or evidence of symptomatic autoimmune disease (e.g., pneumonitis, glomerulonephritis, vasculitis, or other), or history of active autoimmune disease that has required systemic treatment (i.e., use of corticosteroids, immunosuppressive drugs or biological agents used for treatment of autoimmune diseases) in past 2 years prior to enrollment. Replacement therapy (e.g., thyroxine for hypothyroidism, insulin for diabetes or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment for autoimmune disease
- A life threatening (Grade 4) immune related adverse event related to prior immunotherapy.
- Failure to recover from any immune related adverse event from prior anti-cancer therapy to grade ≤ 1, with the exception of alopecia or endocrinopathies that are managed and stable on hormone replacement therapy.
- Failure to recover from any other toxicity (other than immune-related toxicity) related to previous anticancer treatment to Grade ≤ 2 except for alopecia and peripheral neuropathy related to prior chemotherapy.
- Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies) disease that is not controlled
  HIV positive patients will be considered eligible if:

    - Established ART for at least four weeks and have an HIV viral load less than 400 copies/mL prior to enrollment
    - CD4+ T-cell (CD4+) counts ≥ 350 cells/uL
    - No opportunistic infection within the past 12 months
- Patients known to be positive for active Hepatitis B (HBsAg reactive with detectable HBV DNA), or Hepatitis C (HCV RNA (qualitative) is detected)
    - Patients with chronic hepatitis B (positive HBsAg and/or HBcAb and negative HBV DNA by PCR) are eligible for this study if they are on suppressive anti-viral therapy and deemed safe by a gastroenterologist
    - Patient who is HCV Ab positive but HCV RNA negative due to prior treatment or natural resolution will be considered eligible.
- Has a known history of active TB (Bacillus Tuberculosis)
- Women who are pregnant or breastfeeding
- Patients expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of study treatment(s)
- Prior organ transplantation including allogenic stem-cell transplantation
- Active infection requiring systemic therapy
- Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v5 Grade ≥ 3)
- Prior treatment with an investigational anti-ICOS therapy
- Treatment with a PD-1 or PD-L1 antibody within 8 weeks of the start of study therapy.
- Treatment with any other anticancer therapy within 3 weeks of the start of study drug (ie, other immunotherapy, chemotherapy, radiation therapy, etc.).
- Treatment with antibiotics within 14 days prior to first dose of study drug
- Receipt of a live-virus vaccine within 30 days prior to first dose of study drug (vaccines that do not contain live virus are permitted).
- Presence of any other active malignancy requiring systemic therapy that may influence the outcome of this study.

7.0 RECRUITMENT PLAN

7.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed.

The clinical trial will be listed on the clinicaltrials.gov website. Patients will be identified through internal referrals and external referrals by Medical and Surgical Oncologists, nationally and internationally. Patients will be recruited through the Sarcoma Disease Management Team. The Sarcoma Service and

the Sarcoma Disease Management Team each hold weekly interdepartmental meetings to identify study participants for open clinical trials. A patient's sarcoma histological subtype will always be confirmed by a MSK pathologist prior to being deemed fully eligible for this study. We will also discuss the trial and patient recruitment with several Sarcoma patient support groups. The principal investigator will be available to all patients for further questions and information through a contact number, which will be provided on the consent form. All eligible patients, regardless of sex and race, will be approached for participation. The investigators are aware of the NIH policy concerning inclusion of women and minorities in clinical research populations.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center. (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

7.2 Randomization

No randomization will be performed.

8.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form. Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

9.0 PRE-TREATMENT/INTERVENTION

All aspects of the screening evaluation must be completed prior to entering the study, unless otherwise noted. The following must be completed within 28 days of starting treatment:

- Confirmation of disease: documented presence of metastatic and/or locally advanced sarcoma with RECIST v1.1 measurable disease using standard baseline imaging with CT scan of the chest (with or without contrast), abdomen and pelvis (with contrast where renal function permits) and all other known sites of disease and MRI if applicable.
- Signed informed consent for study participation
- Full medical history including all active conditions
- Review of concomitant medications including any prior medications taken
- Physical exam (including height and weight)
- Vital signs (pulse, blood pressure, temperature, respiratory rate, and oxygen saturation). Note: height may be documented at any time prior to registration
- ECOG performance status
- Complete blood count with differential
- Comprehensive metabolic panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total protein, albumin, total bilirubin, total protein, AST, ALT, alkaline phosphatase, calcium), magnesium, and phosphorus
- Amylase, lipase, CK, and LDH
- PT (or INR) and aPTT
- Thyroid function tests (TSH, T4 free, T3)
- Hepatitis B surface antigen and core antibody, and Hepatitis C antibody, with reflex PCR test if positive
- Urinalysis (dipstick)

- Serum β-HCG or urine pregnancy test for women of child-bearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required
- 12-lead electrocardiogram (ECG)
- CT scan of the chest (with or without contrast), abdomen and pelvis (with or without contrast) or MRI and CT scan or MRI of brain, if applicable.
- All patients enrolled in this study will undergo a new baseline biopsy where feasible

10.0 TREATMENT/INTERVENTION PLAN

10.1 Treatment plan

o All patients will be administered the XmAb23104 monotherapy intravenously, as an outpatient, on days 1 and 15 of each 28-day cycle for a total of 24 months.

o For each cycle, XmAb23104 will be administered at the recommended phase 2 dose, 10mg/kg once every two weeks.

- Supportive medications will be administered according to institutional guidelines
- Granulocyte colony stimulating factor (G-CSF) administration will be permitted at the discretion of institutional policy and/or the study investigator
- Physical exam, including vital signs and weight measurement, and toxicity assessments will occur on day 1 and 15 of each treatment cycle and at the end of treatment visit
- Radiographic assessment by RECIST v1.1 will occur at baseline, after the first two treatment cycles, and every 8 weeks for the first 56 weeks of study treatment, followed by every 8-12 weeks thereafter at the discretion of the treating investigator
- Mandatory tumor biopsies will be performed at baseline and week 7

- Peripheral blood analyses will be obtained at baseline, day 1 of cycle 2 and 3, and at the end of treatment
- The end of treatment visit should be within 30 days (+ 7 days) of the last administered dose of study therapy
- Survival status will be confirmed every 12 weeks (± 28 days) following the end of treatment visit until death, the patient withdraws consent, or 12 months after the end of treatment, whichever occurs first.

10.2 Dose Delay Criteria

Because of the potential for clinically meaningful XmAb23104 related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs of selected categories, see Appendices A and B. Tumor assessments should continue per protocol schedule, even if dosing is delayed.

If dosing is delayed and the criteria to resume treatment are subsequently met, the subject should restart treatment one week later or at the discretion of the investigator once criteria are met. If treatment is delayed or interrupted for > 8 weeks, the subject must be permanently discontinued from study therapy, except as specified in Appendices A and B or unless the principal investigator determines that resumption of the drug will provide further clinical benefit.

XmAb23104 should be permanently discontinued if any AE, laboratory abnormality, or intercurrent illness occurs which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued XmAb23104 dosing.

A delay in treatment due to holidays, weather, or other circumstances will be permitted up to 7 days and not considered a protocol violation. Tumor assessments should continue per protocol schedule, even if dosing is delayed.

10.3 Dose Modifications

No dose modification of XmAb23104 will be permitted. Permanent discontinuation criteria for XmAb23104 are outlined in the study appendix.

11.0 EVALUATION DURING TREATMENT/INTERVENTION

11.1 Schedule of Assessments/Study Calendar

Table 1. Study Calendar

	Screening	**Treatment**						**Follow up**	
	Screening	**Cycle 1**		**Cycle 2**		**Cycle 3+**		**End of treatment (EOT)[10]**	**Follow up**
Intervention	**28 Days prior to the treatment**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**30 days after last dose (+7 days)**	**Every 12 weeks**
Informed consent	X								
Medical history	X								
Concurrent medications	X	X	X	X	X	X	X	X	
XmAb23104[1]		X	X	X	X	X	X		
Adverse event assessment		X	X	X	X	X	X	X	

Physical exam[2]	X	X	X	X	X	X	X	X	
CBC with differential	X	X	X	X	X	X	X	X	
Routine laboratory tests[3]	X	X	X	X	X	X	X	X[10]	
Thyroid function tests[4]	X	X		X		X		X[10]	
HBV, HCV serology (reflex PCR if +ve)[5]	X								
Serum pregnancy test[6]	X	X		X		X		X[10]	
Urinalysis	X							X[10]	
EKG	X							X	
CT/MRI[7]	X				X				
Research blood tests[8]	X			X		X		X	
Research biopsy[9]	X				X				
Survival status[11]									X

1. XmAb23104 will be administered via intravenous infusion at assigned dose. The XmAb23104 dosing window for Cycle 1 Day 15 will be ±1 day and ±3 days for Cycle 2 and higher. XmAb23104 will be administered as a 1-hour (-5 min / + 15 min) IV infusion. Supine blood pressure observation period and pulse rate, body temperature, respiratory rate. On days of XmAb23104 infusions, vital signs should be taken pre-infusion and 30 minutes after start of infusion (±10 min), at the end of infusion (±5 min), and 30 and 60 minutes after end of infusion (±10 min), then hourly (±10 min) after end of infusion for the remainder of the required. All vital signs during infusion should be taken with subject in the same position. Subjects will be observed for at least 4 hours following the first 3 infusions. The observation period and vital signs assessments may be decreased to 2 hours if there are no infusion reactions for 3 consecutive infusions.
2. Physical exam includes vital signs (pulse, blood pressure, temperature, respiratory rate, and oxygen saturation), height (required at baseline/screening assessment) and weight, and determination of ECOG status.
3. Routine laboratory tests include comprehensive metabolic panel (sodium, potassium, magnesium, phosphorus, chloride, bicarbonate, BUN, creatinine, glucose, total protein, albumin, total bilirubin, AST, ALT, alkaline phosphatase), and amylase, and lipase to be performed prior to each dose of treatment. In addition, CK, LDH, PT (or INR) and aPPT should be tested during screening and at EOT only.
4. Thyroid function tests include TSH, T3, and FT4. All will be collected at baseline and EOT visits. TSH and free T4 is required at baseline and before each cycle
5. Hepatitis B surface antigen and core antibody, and Hepatitis C antibody, with reflex PCR test if positive
6. Serum β-HCG (Female subject of childbearing potential should have a negative serum pregnancy at screening and within 72 hours prior to first dose of both study drugs, the start of every cycle and at the off-study visit.
7. Standard imaging studies for RECIST 1.1 assessment will be performed at baseline, week 8 and every 8 weeks subsequently (± 7 days window) for 56 weeks following which imaging may be performed every 8-12 weeks at the discretion of the treating investigator. Imaging will include CT of chest (with or without contrast) , CT of abdomen/pelvis (with contrast where renal function permits) and/or MRI alternatively (with and without contrast) of an affected area if deemed necessary by the study investigator.
8. Research blood tests will be collected at baseline, day 1 cycle 2, 3, 4, 6 and at the end of treatment.
9. All study participants will undergo mandatory tumor biopsies at baseline and week 7 (+/-7 days) where feasible and safe to do so. Effort will be made to choose the same site on re-biopsy when clinically feasible.
10. Subjects who are permanently discontinued from receiving investigational product will return for End of Treatment visit 30 days after last dose or prior to initiation of unless consent is withdrawn, the subject is lost to follow-up, or

he/she begins another treatment. If patient begins another treatment, EOT Labs are to be collected prior to initiation of next treatment.

11. Survival status and initiation of new anti-cancer therapy will be collected every 12 weeks (± 28 days) following the end of treatment visit until death, the patient withdraws consent, or 12 months after the end of treatment, whichever occurs first. This information may be obtained in person/via phone/electronically/medical record review.

11.2 Tumor and Blood Samples for Correlative Analysis

11.2.1 Tumor Biopsies

Tumor biopsies for research purposes will be done at baseline and at 7 weeks after treatment where feasible and safe to do so. The same tumor site will be biopsied at each time point, if feasible. Cores will be obtained with 18-gauge needles where appropriate and be of at least 1 cm in length. Cores should be representative of tumor and targeted to the de-differentiated component in the case of dedifferentiated liposarcoma (DD-LPS) and dedifferentiated chondrosarcoma.

The quality, viability, and tumor content of biopsies will be confirmed by the on-call clinical pathologist at the time of retrieval. The goal will be to extract 6 cores, with a minimum of one formalin-fixed, for later paraffin embedding (FFPE), one fresh (stored in RPMI media on ice), and one flash frozen in liquid nitrogen and transported on dry ice. If it is not possible to obtain 6 cores the sample type will be prioritized as follows:

1. FFPE
2. Fresh (stored in RPMI)
3. Flash frozen
4. Fresh (stored in RPMI)
5. Flash frozen
6. Flash frozen

If any extra cores are obtained, they will be flash frozen with liquid nitrogen. Samples will be labeled using an adherent, liquid nitrogen proof label with the following information:

1. Procurement date
2. Study IRB number
3. Study patient number
4. Time point (baseline/pre-treatment, on-treatment (week 8), progression (optional))
5. Anatomical biopsy site

Each FFPE sample is to be placed in a pathology sample container pre-filled with formalin and delivered to the MSK pathology lab. Each fresh sample is to be placed in a 50ml Falcon tube with 20 ml of RPMI media, labeled and the cryovial placed in a sample bag and the sample bag placed within the ice.

Each flash frozen sample is to be placed within an individual cryovial, labeled, and the vial immediately placed in liquid nitrogen for 2 minutes or longer to snap-freeze the tissue. These vials can be transported in either liquid nitrogen or in dry ice. The fresh and flash frozen samples are to be transported to the Immune Monitoring Facility as detailed below in section 11.2.2

11.2.2 Research Blood Sample Collection

Peripheral blood samples for research will be obtained at baseline, day 1 cycle 2, 3, 4, 6 and at the end of treatment. At each research blood collection time point the following samples will be collected:

• 4x8ml of peripheral venous blood will be collected in CPT tubes. Invert all tubes several times immediately after collection to ensure mixing with anticoagulant.

Specimens will be placed in a biohazard bag and transportedat room temperature. Samples will be labeled with the following information without obstructing the visualization of drawn blood volume:

- Procurement date
- Study IRB number
- Study patient number
- Patient medical record number
- Time point (baseline or week-X)

1. Research blood samples and tumor biopsy samples, along with completed requisition forms, are to be transported to the Immune Monitoring Facility located at the MSKCC Zuckerman Research Center (408 E. 69th St, New York, NY 10021), Room Z-1513. Place into sample drop-off bin located OUTSIDE of Z-1513. At least 24h advanced notification should be provided using the Outlook shared blood delivery calendar (zzCAL_LAB_Clinical_Trials/Shared Calendar) and be sure to include clinical site location and contact information from which samples are arriving on the calendar notice.
    a. Rosemarie Ramsawak ramsawar@mskcc.org
    b. Phillip Wong wongp@mskcc.org

Samples must be delivered after collection between the hours of 9 am-4 pm to a member of the lab.

11.3 Biomarker Analysis

11.3.1 Density of Immune Infiltrate and Immune Regulatory Biomarker Expression

IHC will be used to assess the number and composition of immune infiltrates to define the immune cell subsets present within the tumor before and after exposure to study therapy. PD-L1 and ICOS expression within the tumor and on immune cells before and after exposure to study therapy will also be determined. IHC assays will be performed using, but are not limited to, the following markers: CD3, CD4, CD8, CD25, CD28 CD45RA, CD68, CD69, CD163, CD206, CCR7, IDO-1, PD-L1, PD-1, CD137, FOXP3, LAG-3, TIM-3, and ICOS.

11.3.2 Tumor Biopsy gene expression profiling

Fresh tumor biopsy will be examined for RNA gene and protein expression by NanoString technology (nCounter® RNA: Protein, PanCancer Immune Profiling Panel) and/or qRT-PCR to detect expression of immune related genes. This panel includes 770 immune related genes including: 109 genes related to cell surface markers for 24 different immune cell types and populations, 30 genes for commonly studied cancer/testis (CT) antigens, over 500 genes for measuring immune response and 40 reference genes.

In the course of this research it is possible that some patients whose tumors are analyzed through investigational “next-generation” profiling in a research (non-CLIA) environment will be found to have

somatic or germline mutations in genes that are known to be associated with an increased risk of cancer or other diseases. It will be stated in the consent that the participants will not receive any specific results from research tests. The consent will tell participants that if they wish to have genetic testing done for personal reasons than they should make an appointment with the MSK Clinical Genetics Service.

If in the course of this research a research finding is obtained that, in the opinion of the investigator, may be critical to the preventive care of the participant or their family, the investigator can communicate that finding to the IRB Genomic Advisory Panel (GAP). The finding will be reviewed by the GAP to determine whether the incidental finding should be discussed with the participant. For MSK, in the event that the GAP determines that the finding should be discussed with the participant, and the participant has consented to be re-contacted, then the treating/consenting physician shall be contacted by the panel and asked to refer the participant to the Clinical Genetics Service for further discussion of the research finding.

11.3.3 Next generation sequencing for T-cell receptor clonality in TILs

Samples will be analyzed using high throughput sequencing of the variable β-chain of the T cell receptor (TCR) to characterize the expansion and clonality of the T-cell repertoire in TILs.

11.3.4 Peripheral Blood Immunophenotyping, Functional Analyses, and Cytokine/Chemokine Analysis

Samples will be analyzed by flow cytometry to study the effects of XmAb23104 monotherapy on various peripheral blood immune cell subsets including, but not limited to T cell subsets (activated, memory and regulatory T cells). To explore whether targeting PD1 and ICOS will restore T cell activation and function, peripheral blood mononuclear cells (PBMCs) will be isolated and cryopreserved. Assays of the functional status of effector T cells will be performed, including, but not limited to assays for interferon-gamma (IFN-γ) and granzyme B.

Baseline and on-treatment serum levels of chemokines, cytokines and other immune mediators will be assessed by techniques that may include, but are not limited to, ELISA or multiplex assays. Analytes may include, but are not limited to IFN-γ, IL-12, IL-10, soluble MICA, C-reactive protein, soluble PD-1, ICOS and soluble PD-L1.

12.0 CRITERIA FOR REMOVAL FROM STUDY

In the absence of serious toxicity or complications, all patients will continue treatment. In the absence of treatment delays due to AEs, treatment may continue until one of the following criteria applies:

- Disease progression
- Development of an inter-current medical condition or need for concomitant treatment that precludes further participation in the trial
- Unacceptable toxicity or any AE that precludes further participation in the trial.
- The investigator removes the patient from the trial in the best interests of the patient
- Patient death
- Study completion or discontinuation for any reason
- Patient withdraws consent to continued participation in the trial or is lost to follow up

Due to the mechanism of action, patients may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of XmAb23104. The patient may be allowed to continue study treatment after initial RECIST 1.1 defined progression if they are assessed by the treating physician to be deriving clinical benefit and tolerating study treatment and have no signs of symptoms indicating clinically significant progression of disease and no decline in ECOG performance status. Patients who are treated beyond progression will be re-consented and adequately informed of all FDA-approved therapy, and potential clinical benefit, that the patient may be foregoing in order to continue receiving the investigational product at the time of radiographic progression. Such patients should discontinue study therapy upon further evidence of progression at the discretion of the treating investigator.

Subjects who are permanently discontinued from receiving investigational product will return for end of treatment visit, unless consent is withdrawn, the subject is lost to follow-up, or he/she begins another treatment. All subjects will be followed for survival by phone (if not actively following at MSKCC) every 3 months for up to 12 months. After the end of treatment, each patient will be followed for 30 days for AE monitoring. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported. If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Criteria for Therapeutic Response/Outcome Assessment

13.1.1 Categorization of Tumor Lesions

- Measurable Lesions: must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
    - 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
    - 10 mm caliper measurement by clinical exam (when superficial)
    - Malignant lymph nodes are 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 no greater than 5 mm).
- Non-measurable Lesions: 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). Lesions considered truly non-measurable including leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
- Target Lesions: all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- Non-target Lesions: it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases")

13.1.2.1 Evaluation of Target Lesions

- Complete Response (CR): disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be “0” if there are target nodes.
- Partial Response (PR): at least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): at least a 20% increase in the sum of diameters 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. (Note: the appearance of one or more new lesions is also considered progression.)
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

13.1.2.2 Evaluation of Non-target Lesions

- Complete Response: disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis)
- Non-complete response/Non-progressive disease: persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease: unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from “trace” to “large,” an increase in lymphangitic disease from localized to widespread.

13.1.4 Appearance of New Lesions

The appearance of new lesions is considered PD according to RECIST v 1.1 guidelines. Considering the unique response kinetics that have been observed with immunotherapy, new lesions may not represent true disease progression. In the absence of rapid clinical deterioration, subjects may continue to receive study treatment.

13.1.5 Evaluation of Overall Response

Table 2 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Table 2: Evaluation of Overall Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Not evaluable (NE)[1]	No	PR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD and NE	No	PR
SD	Non-PD and NE	No	SD
Not All Evaluated	Non-PD	No	NE
PD	Any	Yes/No	PD
Any	PD	Yes/No	PD
Any	Any	Yes	PD

13.2 Criteria for Study Endpoint Evaluability

Patients evaluable for efficacy analysis will include all patients treated with XmAb23104 who are assessable for response. Patients who have no assessment of response post-baseline will not be considered evaluable for response unless they missed the assessment due to progression of disease, death or treatment-related toxicities, in which case they will be considered non-responders for that time point. Patients with at least one post-baseline assessment who are not assessed at 24 weeks for reasons other than progression of disease, death, or excessive-toxicity, will be evaluated based on their last imaging assessment. Patients who are not evaluable (excluding those who died, had progression of disease, stopped study treatment due to treatment-related toxicity, or those with at least one post-baseline assessment) may be replaced. The anticipated replacement rate is ≤ 5%. Patients evaluable for safety analysis will include all patients who have received at least one dose of with XmAb23104.

14.0 BIOSTATISTICS

This is a single-center, open label, phase II trial to evaluate the XmAb23104 monotherapy. Confirmed response rate over the first 24 weeks of treatment is our primary endpoint. All treatment decisions and the evaluation of the primary endpoint will be based on RECIST v1.1. Patients will be stratified into one of 6 cohorts based on sarcoma histological subtype. There will be 5 patients in each cohort.

14.1.1 Primary Endpoint

*T*o evaluate the efficacy, as assessed by best objective response rate (ORR; partial response [PR] and complete response [CR]) at 24 weeks, as defined by RECIST v1.1, of XmAb23104 in patients with advanced sarcoma. ORR will be calculated as a proportion with a two-sided 95% confidence interval provided.

14.1.2 Hypothesis

We are testing the hypothesis of an objective response rate with XmAb23104 being at most 5% (clinically inactive) versus an objective response rate of at least 25% (clinically active).

14.1.3 Design Characteristics and Endpoint Assessment

This study will enroll a total of 30 evaluable patients. Demonstration of at least 4 objective responses will be considered as having sufficient evidence of promising activity in this population. This design yields 96% power to detect a true objective response rate of at least 25%, with a 0.06 significance level (1-sided test) if the true objective response rate is 5%.

The statistical consideration for this study will be for all 30 patients enrolled to one of 6 disease-specific cohorts: SFT, LMS, dedifferentiated chondrosarcoma, UPS/MFS, translocation associated sarcoma including SEF or extraskeletal myxoid chondrosarcoma (ESMC) and Pecoma. As each histologic subtype may respond differently to treatment with XmAb23104, 5 patients per histology-specific cohort will be enrolled, for a total of 30 patients. The sample size of 30 was chosen to allow the opportunity to detect a significant difference in ORR within each sarcoma subtype under investigation and because of budget constraints. All 6 cohorts will be evaluated together for the primary and secondary endpoints. If a signal of efficacy is found within a specific histologic subtype as opposed to others, expansion of this cohort or a larger phase II study may be considered, depending on discussions between the study investigators and the sponsor based on both efficacy data and correlatives results. A signal of efficacy in a given sarcoma subtype, for the purpose of determining appropriateness of expanding the study will be considered as either of the following: 1) two objective responses or 2) a single objective response in combination with correlative data where available to support a positive therapeutic effect or manipulation of the immune microenvironment.

If a two-stage design were implemented, the study might be terminated early for a presumed lack of efficacy that may be driven by one or two histologic subtypes, especially if the accrual rate for different histologies differs. As sarcoma represents a heterogenous group of diseases with unique biologies, the response to dual-immune checkpoint blockade may be different in each histologic cohort. Response to single-agent anti-PD-1 therapy varies by subtype, these have been relatively small early phase trials and results have not been consistent or uniform across studies.

We hypothesize that XmAb23104 will yield an ORR of 25% if clinically active versus 5% if clinically inactive in advanced sarcoma.

Based on the available clinical trial data, we would connsider an ORR of 25% at 24 weeks to be promising and 5% ORR to be not promising. The study will be claimed to be positive if 4 or more of the 30 evaluable patients demonstrate a confirmed objective response at 24 weeks. This design has a type I error rate of 0.06 and a power of 96%.

The primary efficacy dataset will include all patients who received at least one dose of study therapy and are assessable for response. Patients who have no assessment of response post-baseline will not be considered evaluable for response unless they missed the assessment due to progression of disease, death or treatment-related toxicities, in which case they will be considered non-responders for that time point.
The study is expected to complete accrual in 30 months. Accrual is expected to vary based on histological sarcoma subtype, likely 1 patient every 2 months for the cohorts enrolling leiomyosarcoma and dedifferentiated liposarcoma and 1 patient every 4-6 months for cohorts enrolling all other subtypes. The accrual rate will be monitored closely and every 6 months consideration will be made to potentially stop enrolling a specific sarcoma subtype and expand enrollment of another sarcoma subtype based on accrual patterns observed.

14.1.4 Secondary Endpoints

- To evaluate the safety and tolerability of XmAb23104 in patients with advanced sarcoma.

Adverse events will be recorded using NCICTCAE v5.0 criteria and the adverse event rate to study treatment will be determined. Categorical data analysis will be used to summarize the adverse event rate and maximum severity during treatment for each patient and AE classification

The safety analysis dataset will include all patients treated with at least one dose of XmAb23104.

- To evaluate the efficacy, as assessed by the clinical benefit rate(stable disease [SD] for ≥ 16 weeks + PR at 48 weeks + CR at 48 weeks) , as defined by RECIST v1.1, of XmAb23104 in patients with advanced sarcoma. Patients who don't have the 48-week assessment due to reasons other than progression, excessive toxicity, or death, will be included in the calculation of 48-week CBR by carrying forward the last assessment before 48 weeks,
- To assess the progression free survival (PFS) rate at 6 months, overall survival (OS) at 12 months, median PFS, and median OS for patients treated with XmAb23104 in patients with advanced sarcoma
- To assess the duration of response, as defined by RECIST v 1.1 of XmAb23104 in patients with advanced sarcoma.

Kaplan-Meier methodology will be used to evaluate time to event endpoints: PFS (time from treatment start date to the earliest of either disease progression or death from any cause), OS (time from treatment start date to death from any cause) and duration of response (time from first response to disease progression). CBR will be calculated as a proportion with a two-sided 95% confidence interval provided.

14.1.5 Exploratory Endpoints

- To determine the baseline characteristics of sarcoma tumors (pre-treatment biopsy sample) evaluated in this study including level of PD-1/PD-L1/ICOS expression, presence of tumor infiltrating lymphocytes (TILs) and tumor antigens, gene expression profile and T-cell receptor clonality in TILs.
- To assess the potential effect of XmAb23104 on selected biomarker expression measured in post-treatment tumor tissue and the association between these biomarkers (baseline level of expression and the change in biomarker level of expression following treatment) and clinical outcome, including characterization of PD-1/PD-L1/ICOS expression, TILs, gene expression profiling, and characterization of T-cell receptor clonality in TILs.
- To evaluate the associations between selected biomarkers measured in serial peripheral blood and clinical efficacy, including immunophenotyping and functional analyses, evaluation of serum levels of chemokines, cytokines and other immune mediators, and characterization of T-cell receptor clonality in peripheral blood

All patients enrolled on this study will undergo mandatory treatment biopsies both before and after initiation of study therapy. The correlative analyses are exploratory in nature and are not powered to detect specific hypotheses. Results will be used to identify biomarkers of interest that have the potential to define benefit from study treatment**.**

Summary statistics will be used to describe changes over time observed in tumor tissue biopsies (baseline and on-treatment) and serial peripheral blood samples (at baseline, day 1 cycle 2, 3, 4, 6 and at the end of treatment). In addition, the time course of biomarker measurements will be investigated graphically, by summary plots or individual patient plots; their trends over time will be categorized either by visual inspection (if there are clear trend groups such as monotonically increasing or monotonically decreasing) or by pattern recognition methods such as K-means clustering. The associations with the observed trend categories in selected biomarkers will be evaluated for association with clinical outcome such as response, if there are a reasonable number of events for each outcome, using Fisher's exact test, and progression free survival using log rank test.

15.0 ADVERSE EVENTS/RISKS

15.1.1 Definition of an Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse.

All AEs, either reported by the patient or observed by study staff, will be recorded for up to 30 days after

end of treatment or until a new antineoplastic regimen has been initiated. AEs will be summarized by preferred term, system organ class, NCI CTCAE version 5.0 grade of severity, and relationship to each study drug.

Examples of events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE).

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease or condition present or detected at the start of the study that do not worsen.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.

Any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition, are not to be reported as AEs or SAEs.

15.1.2 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the protocol.

15.1.3 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. These could include overall disease progression or pain or discomfort caused by growing tumors. Such events do not meet the definition of an Adverse Event unless assessed to be more severe than expected for the patient's condition. An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as an SAE. Deaths and hospitalizations related to disease (other than for study procedures) during the study period and 90 days after completion must be reported as SAEs.

Disease Related Events that would qualify as an Adverse Event or Serious Adverse Event, include any

event based on the underlying disease that is worse than expected as assessed by the investigator for the patient's condition if the investigator believes there is a causal relationship between the investigational product/study treatment/protocol required therapies and disease worsening.

15.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

15.2.1 External SAE Reporting

The MSK SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office. Regardless of suspected causality (e.g., relationship to study drug or study procedures), all SAEs occurring after the participant initiates treatment through 30 days after the last dose of study drug must be reported to Xencor (or designee) within 24 hours of learning of its occurrence, unless otherwise specified by the Protocol. Information regarding maternal exposure to the Study Drug during pregnancy, and information regarding paternal exposure to the Study Drug (in accordance with MSK pregnant partner policy) will be reported to Xencor according to the reporting timelines below.

•Procedures for Reporting SAEs/AEs and Exposure to Study Drug During Pregnancy to Xencor/designee

Pregnancy alone is not regarded as an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be regarded as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. All notifications of pregnancy should be documented and reported through 30 days following cessation of study treatment (or through 28 days following cessation of study treatment, if the subject initiates new anticancer therapy) whether or not there is an associated AE or SAE.

Each pregnancy must be reported by the Investigator to Xencor using an initial pregnancy report form within 24 hours after becoming aware of the pregnancy. The Investigator must follow-up and document the course and the outcome of all pregnancies even if the subject was withdrawn from the clinical study or if the clinical study has finished. The follow-up period will be deemed to have ended when the health status of the child has been determined on its birth.
All outcomes of pregnancy must be reported by the Investigator Xencor on the pregnancy outcome report form within 30 days after he/she has gained knowledge of the normal delivery or elective abortion.
Any SAE that occurs during pregnancy must be recorded on the SAE report form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours of awareness in accordance with the procedure for reporting SAEs.

- <u>Initial Reporting:</u>

  - Upon learning of an SAE temporally associated with the Study Drug or exposure to Study Drug during pregnancy, which is required to be reported pursuant to Applicable Law, Institution or Principal Investigator shall complete and submit an Adverse Event Report Form to Xennor or its designee within twenty-four (24) hours of learning of the event, via email to icon-mads@iconplc.com.

- If critical or outstanding information is missing from the Adverse Event Report Form or additional clarification is needed, Xencor or its designee shall submit a Data Clarification Form ("DCF") to the Institution or Principal Investigator.

o Follow-up Reporting:

- When new information regarding an initially reported SAE temporally associated with the Study Drug or maternal or paternal exposure to Study Drug during pregnancy becomes available, the Institution or Principal Investigator shall provide such follow-up information on a new or updated Adverse Event Report Form within five (5) business days of learning of the new information, via icon-mads@iconplc.com.

o Form:

- All adverse event information is reported to Xencor/designee on the Principal Investigator's/Institution's Adverse Event Report Form. The Principal Investigator does not provide medical records (e.g., discharge summary) to Incyte, unless specifically requested.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential drug-induced liver injury (DILI), meeting the defined criteria, must be reported as SAEs).

15.3 Possible Toxicity

15.3.1 XmAb23104

To date, XmAb23104 has been evaluated in a single Phase 1 dose-escalation trial (XmAb23104-01) in adults with advanced solid tumors. This trial is ongoing, and a recommended Phase 2 dose of 10 mg/kg was established; an MTD was not reached.

As of the data cutoff date of 01 November 2021, a total of 75 patients have been enrolled and treated in the XmAb23104-01 study. Doses of XmAb23104 have ranged from 0.002 – 15.0 mg/kg.
Four subjects were eligible and opted to intra-subject dose escalate; 1 subject from 0.2 mg/kg to 0.6 mg/kg, 1 subject from 0.6 mg/kg to 1.8 mg/kg, 1 subject from 5.4 mg/kg to 10 mg/kg and a single subject escalated twice, once from 1.8 mg/kg to 5.4 mg/kg and finally up to 10 mg/kg. Three subjects received 10 mg/kg XmAb23104 monotherapy in the expansion phase of the study, and 10 subjects received 10 mg/kg XmAb23104 in combination with 1 mg/kg ipilimumab.
Sixty-seven (89.3%) subjects had at least 1 treatment-emergent adverse event (TEAE); the most common was fatigue, observed in 17 (22.7%) subjects. In addition, 9 (12.0%) subjects experienced immunotherapy-related AEs (IRAEs) and 1 (1.3%) subject experienced an infusion-related reaction (IRR).

The mean half-life of XmAb23104 is approximately 10.6 days. Insufficient data are available at this time to accurately define efficacy and PD.

The safety findings based on the 75 subjects treated in the XmAb23104-01 study have shown acceptable toxicity.

Study XmAb23104-01 is a Phase 1, FIH, multiple-dose, ascending dose-escalation (Part A) and cohort expansion (Part B) study. The primary objectives of XmAb23104-01 are to (1) evaluate the safety and tolerability of XmAb23104 with and without ipilimumab in subjects with selected advanced solid tumors who have progressed after treatment with standard/approved therapies or have no appropriate available therapies, and (2) identify the MTD and/or RD/schedule for XmAb23104 administered by IV dosing on Days 1 and 15 of each 28-day cycle in subjects with selected advanced solid tumors.
As of the clinical database cutoff of 01 November 2021, sixty-two subjects have been treated at dosages of < 10, 10, and 15 mg/kg in escalation (Part A). Thirteen subjects have received 10 mg/kg XmAb23104 with or without 1 mg/kg ipilimumab in expansion (Part B).

Of the 75 subjects dosed with study drug, 21 (28%) subjects experienced a total of 33 TE-SAEs. The most frequent TE-SAEs were from the following system organ classes (SOCs): Gastrointestinal disorders in 6 (8.0%) subjects, Renal and urinary disorders in 4 (5.3%) subjects, and Investigations and Respiratory, thoracic and mediastinal disorders in 3 (4.0%) subjects.
As of 01 November, 2021, there were 2 cases of serious adverse reactions (SARs; assessed by the sponsor as possibly related to the IMP) reported in 2 (2.7%) subjects in the XmAb23104-01 study. These events included a Grade 3 Hyperbilirubinemia reported in a subject at 1.8 mg/kg dose, and asymptomatic Grade 4 Lipase increased in a subject at 0.6 mg/kg dose, both of which resolved. No fatal or life-threatening SARs were reported.
At least 1 TEAE occurred in 89.3% of subjects. The most commonly observed TEAEs were fatigue (18 subjects, 24.0%), nausea (18 subjects, 24.0%), vomiting (15 subjects, 20.0%), diarrhea (14 subjects, 18.7%), pyrexia (13 subjects, 17.3%), and anemia (12 subjects, 16.0%) [see Appendix A, Table 14]. • Treatment-related AEs (TRAEs) are shown in Table 3. By patient, the most common events were diarrhea (9 subjects, 12%), fatigue (7 subjects, 9.3%), decreased appetite (7 subjects, 9.3%), pyrexia (7 subjects, 9.3%), and vomiting (6 subjects, 8.0%) • Grade ≥ 3 TRAE occurred in 8 (10.7%) subjects. The most common Grade ≥ 3 TRAEs were lipase increased and diarrhea, each seen in 2 (2.7%) subjects. • There were 15 IRAEs, as determined by the investigator, occurring in 9 subjects reported thus far in the study. No individual IRAE occurred in more than 1 subject.

Table 3. Treatment-Related Adverse Events by Preferred Term in Decreasing Frequency (Safety Population)

	XmAb23104 Monotherapy					XmAb23104 + Ipilimumab	
	Escalation			Expansion	Escalation+ Expansion	Expansion	
Preferred Term, n(%)	**<10 mg/kg (N = 49)**	**10 mg/kg (N = 10)**	**15 mg/kg (N = 3)**	**10 mg/kg (N = 3)**	**All Doses (N = 65)**	**10 mg/kg (N = 10)**	**Study Overall (N = 75)**
Number of subjects with at least one event	32 (65.3)	4 (40.0)	1 (33.3)	0	37 (56.9)	6 (60.0)	43 (57.3)
Diarrhoea	6 (12.2)	0	0	0	6 (9.2)	3 (30.0)	9 (12.0)
Decreased appetite	4 (8.2)	2 (20.0)	0	0	6 (9.2)	1 (10.0)	7 (9.3)
Fatigue	5 (10.2)	1 (10.0)	0	0	6 (9.2)	1 (10.0)	7 (9.3)
Pyrexia	4 (8.2)	0	0	0	4 (6.2)	3 (30.0)	7 (9.3)
Vomiting	4 (8.2)	0	0	0	4 (6.2)	2 (20.0)	6 (8.0)
Headache	3 (6.1)	1 (10.0)	0	0	4 (6.2)	1 (10.0)	5 (6.7)
Nausea	3 (6.1)	1 (10.0)	0	0	4 (6.2)	1 (10.0)	5 (6.7)
Rash maculo-papular	2 (4.1)	2 (20.0)	1 (33.3)	0	5 (7.7)	0	5 (6.7)
Chills	3 (6.1)	0	0	0	3 (4.6)	1 (10.0)	4 (5.3)
Lipase increased	4 (8.2)	0	0	0	4 (6.2)	0	4 (5.3)
Pruritus	3 (6.1)	0	1 (33.3)	0	4 (6.2)	0	4 (5.3)
Rash	3 (6.1)	1 (10.0)	0	0	4 (6.2)	0	4 (5.3)
Amylase increased	3 (6.1)	0	0	0	3 (4.6)	0	3 (4.0)
Constipation	3 (6.1)	0	0	0	3 (4.6)	0	3 (4.0)
Dysgeusia	2 (4.1)	1 (10.0)	0	0	3 (4.6)	0	3 (4.0)
Myalgia	2 (4.1)	1 (10.0)	0	0	3 (4.6)	0	3 (4.0)
Abdominal pain upper	1 (2.0)	0	0	0	1 (1.5)	1 (10.0)	2 (2.7)
Anaemia	1 (2.0)	0	0	0	1 (1.5)	1 (10.0)	2 (2.7)
Dizziness	1 (2.0)	0	0	0	1 (1.5)	1 (10.0)	2 (2.7)
Dyspepsia	1 (2.0)	1 (10.0)	0	0	2 (3.1)	0	2 (2.7)
Gamma-glutamyltransferase increased	2 (4.1)	0	0	0	2 (3.1)	0	2 (2.7)
Hypokalaemia	0	0	0	0	0	2 (20.0)	2 (2.7)

	XmAb23104 Monotherapy					XmAb23104 + Ipilimumab	
	Escalation			Expansion	Escalation+ Expansion	Expansion	
Preferred Term, n(%)	**<10 mg/kg (N = 49)**	**10 mg/kg (N = 10)**	**15 mg/kg (N = 3)**	**10 mg/kg (N = 3)**	**All Doses (N = 65)**	**10 mg/kg (N = 10)**	**Study Overall (N = 75)**
Hyponatraemia	2 (4.1)	0	0	0	2 (3.1)	0	2 (2.7)
Hypophosphataemia	1 (2.0)	0	0	0	1 (1.5)	1 (10.0)	2 (2.7)
Hypothyroidism	1 (2.0)	0	0	0	1 (1.5)	1 (10.0)	2 (2.7)
Rash macular	1 (2.0)	1 (10.0)	0	0	2 (3.1)	0	2 (2.7)
Weight decreased	1 (2.0)	0	0	0	1 (1.5)	1 (10.0)	2 (2.7)
Abdominal pain	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Alanine aminotransferase increased	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Arthralgia	0	1 (10.0)	0	0	1 (1.5)	0	1 (1.3)
Aspartate aminotransferase increased	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Blood bilirubin increased	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Blood corticotrophin increased	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Bronchospasm	0	0	0	0	0	1 (10.0)	1 (1.3)
Candida infection	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Cough	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Dermatitis	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Dry skin	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Dyspnoea	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Early satiety	0	1 (10.0)	0	0	1 (1.5)	0	1 (1.3)
Erythema	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Flank pain	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Flatulence	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Hyperbilirubinaemia	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Hyperglycaemia	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Hyperhidrosis	0	0	0	0	0	1 (10.0)	1 (1.3)
Influenza like illness	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)

	XmAb23104 Monotherapy					XmAb23104 + Ipilimumab	
	Escalation			Expansion	Escalation+ Expansion	Expansion	
Preferred Term, n(%)	**<10 mg/kg (N = 49)**	**10 mg/kg (N = 10)**	**15 mg/kg (N = 3)**	**10 mg/kg (N = 3)**	**All Doses (N = 65)**	**10 mg/kg (N = 10)**	**Study Overall (N = 75)**
Infusion related reaction	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Insomnia	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Lip swelling	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Lymphocyte count decreased	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Muscle spasms	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Muscular weakness	0	0	0	0	0	1 (10.0)	1 (1.3)
Neuropathy peripheral	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Night sweats	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Oedema peripheral	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Pain in extremity	0	1 (10.0)	0	0	1 (1.5)	0	1 (1.3)
Periorbital oedema	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Pneumonitis	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Skin injury	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Vision blurred	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
White blood cell count decreased	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Uncoded	0	0	0	0	0	1 (10.0)	1 (1.3)

Notes:
Adverse event terms were coded using MedDRA version 24.1. Percentages are based on safety population in each column.
For the combination therapy, AEs related to either XmAb23104 or ipilimumab are included.

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15.3.2 Infusion related Reactions

One subject experienced a Grade 2 IRR 30 minutes into the Cycle 2, Day 1 infusion. They were treated with IV antihistamine, solumedrol, and IV fluids, with resolution of the event. On subsequent doses, the patient was premedicated with diphenhydramine, ranitidine, and acetaminophen, with no further IRR events. Infusion reactions have also been commonly seen with monovalent therapeutic antibodies. Infusion reactions to XmAb23104 will be managed as specified in detail in the clinical protocol and/or as deemed appropriate by investigators, including discontinuation of further infusions, if necessary.

Primary prophylaxis with acetaminophen and an H2-blocker should be strongly considered for participants who have had previous systemic reactions to protein product infusions or when recommended according to institutional policy. Secondary prophylaxis is recommended for participants who have experienced IRRs to XmAb23104. Participants who experience life- threatening IRRs should not be retreated with XmAb23104.

Refer to appendix A for guidance on management of suspected infusion reactions.

15.3.2 Immune-Related Adverse Events (irAE)

XmAb23104 is a bispecific humanized mAb that has been designed to restore T-cell immune function, similar to other PD-1 inhibitors that have been extensively studied. Therefore, safety experience with **other drugs** should be considered when administering XmAb23104. Potentially serious irAEs include:

- Pneumonitis
- Hepatitis
- Colitis
- Nephritis
- Endocrinopathies (thyroiditis, hypophysitis, type I diabetes)
- Encephalitis
- Myocarditis
- Skin reactions (including SJS/TEN)
- Rejection of organ transplants
- Other reactions (including arthritis, uveitis, Gulian-Barre syndrome, myasthenia gravis, vasculitis, pancreatitis, and hemolytic anemia)

There were 15 irAEs occurring in 9 subjects reported thus far in the XmAb23104-01 study (see Table 4). Patients will be evaluated for signs and symptoms of irAEs prior to administration of each dose of study drug. Refer to appendix B for guidance on management of immune mediated adverse events.

Table 4 Immune-Related TEAEs by Preferred Term in Decreasing Frequency

	XmAb23104 Monotherapy					XmAb23104 + Ipilimumab	
	Escalation			Expansion	Escalation+ Expansion	Expansion	
Preferred Term, n(%)	**<10 mg/kg (N = 49)**	**10 mg/kg (N = 10)**	**15 mg/kg (N = 3)**	**10 mg/kg (N = 3)**	**All Doses (N = 65)**	**10 mg/kg (N = 10)**	**Study Overall (N = 75)**
Number of subjects with at least one event	6 (12.2)	1 (10.0)	1 (33.3)	0	8 (12.3)	1 (10.0)	9 (12.0)
Alanine aminotransferase increased	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Aspartate aminotransferase increased	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Blood bilirubin increased	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
COVID-19	0	1 (10.0)	0	0	1 (1.5)	0	1 (1.3)
Diarrhoea	0	0	0	0	0	1 (10.0)	1 (1.3)
Hyperglycaemia	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Hypothyroidism	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Infusion related reaction	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Lip swelling	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Lipase increased	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Periorbital oedema	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Pneumonitis	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Pruritus	0	0	1 (33.3)	0	1 (1.5)	0	1 (1.3)
Rash	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)
Rash macular	1 (2.0)	0	0	0	1 (1.5)	0	1 (1.3)

Notes:
Adverse event terms were coded using MedDRA version 24.1. Percentages are based on safety population in each column.

15.3.1.3 Immunagenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of ADA positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

Using a validated electro chemiluminescent assay, anti-XmAb23104 antibodies were induced or boosted in 50 of 69 subjects (72.5%) at any time after treatment. Four of those subjects had preexisting antibodies that were boosted after exposure to XmAb23104. There was an apparent impact on XmAb23104 drug exposure on 2 out of 49 subjects who were screened positive (4.0%) and both were at low-dose (≤ 0.06 mg/kg) cohorts with PK data available and concurrent with confirmed binding ADA, all of which emerged at C1D15 or later with titer greater than 1:5000. Among all subjects treated as of the data cutoff, 1 experienced an infusion-related reaction (Grade 2); this subject was ADA positive. The neutralizing capacity of the antibodies has not been evaluated.

15.3.1.3 Drug Interactions

There are no known drug interactions with XmAb23104, and drug interaction studies have not been conducted. Careful attention is warranted in combination studies since immune-related toxicities may potentially be exacerbated when XmAb23104 is combined with other immunoactive agents. Immunosuppression in excess of physiologic maintenance corticosteroid doses (> 10 mg of prednisone or equivalent) within 14 days of first dose and throughout the treatment period of the study (with the exception of acute treatment for an AE).

Live vaccines within 28 days before first administration of study drug, throughout the treatment period of the study, and for a duration of 90 days after the last dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

15.3.1.6 Contraindications

Patients with known hypersensitivity to recombinant proteins or any excipient contained in the XmAb23104 drug formulation that cannot be controlled with routine supportive measures should not receive XmAb23104.

15.3.1.7 Mutagenicity

XmAb23104 should not be used in females who are pregnant or breastfeeding. XmAb23104 is not expected to be mutagenic; however, carcinogenicity studies have not been conducted, and male participants should use barrier contraception (i.e., condom) while receiving XmAb23104.

16.0 PROTECTION OF HUMAN PARTICIPANTS

16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB). The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

16.2 Data Management

A Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure Medidata database. Source documentation will be available to support the computerized patient record. Final data sets for publication are required to be locked and stored centrally for potential future access requests from outside entities.

16.3 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.4 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research. During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C

have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

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18.0 APPENDICES

18.1 Appendix A Guidelines for Management of Suspected Infusion Reactions

Infusion or hypersensitivity reactions may be observed with administration of any foreign protein. Premedication with an antipyretic (e.g., acetaminophen/paracetamol) and a histamine blocker (e.g., diphenhydramine) should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy. Routine prophylaxis is not required. Guidelines for management of suspected infusion reactions are provided in Appendix A Table 2 below.

Infusion-related reactions and cytokine release syndrome will be toxicity graded according to the NCI-CTCAE, Version 5.

Table 1: Grading of Infusion Reactions/Cytokine Release Syndrome

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics,IV fluids); prophylactic medications indicated for ≤ 24 h	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms followinginitial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated

Cytokine release syndrome	Mild reaction; infusion interruptionnot indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics,IV fluids); prophylactic medications indicated for ≤ 24 h	Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms followinginitial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening; consequences; pressor or ventilatory supportindicated

h = hours; IV = intravenous; NSAIDS = nonsteroidal anti-inflammatory drugs.

REMARK: *An acute infusion-related reaction may occur with an agent that causes cytokine release (eg, monoclonalantibodies 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; Urticaria (hives, welts, wheals); Vomiting.*

The following are treatment guidelines for XmAb23104 treatment-related infusion-relatedreactions:

Table 2: XmAb23104 Infusion Reaction Dose Modification and Treatment Guidelines

NCI-CTCAE Grade	Treatmen t	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusioninterruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicateduntil the participant is deemed medically stable in the opinion of the investigator.	None

Grade 2
Requires therapy or infusion interruption butresponds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.
	• **Stop Infusion.**
	  ○ Additional appropriate medical therapy may includebut is not limited to:
	  ○ IV fluids
	  ○ Antihistamines
	  ○ NSAIDs
	  ○ Acetaminophen
	  ○ Narcotics
	• Increase monitoring of vital signs as medically indicateduntil the participant is deemed medically stable in the opinion of the investigator.
	• If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h. to 50 mL/h.). Otherwise dosing will be held until symptoms resolve andthe participant should be premedicated for the next scheduled dose.
	Participants who develop Grade 2 toxicity despite adequatepremedication should be permanently discontinued from further study drug treatment
		Participant may be premedicated 1.5 h (± 30 minutes) prior to infusion ofdrug with:
		• Diphenhydramine 25-50 mgiv
		• Acetaminophen 650 mg po
		• Corticosteroids (dexamethasone 10 mg iv orequivalent)

Grades 3 or 4
 	
Grade 3:
Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicatedfor other clinical sequelae (eg, renal impairment, pulmonary infiltrates)
Grade 4:
Life-threatening; pressor or ventilatorsupport indicated
	• **Stop Infusion.**
	• Additional appropriate medical therapy may include but isnot limited to:
	  ○ Epinephrine**
	  ○ IV fluids
	  ○ Antihistamines
	  ○ NSAIDs
	  ○ Acetaminophen
	  ○ Narcotics
	  ○ Oxygen
	  ○ Pressors
	  ○ Corticosteroids
	• Increase monitoring of vital signs as medically indicateduntil the participant is deemed medically stable in the opinion of the investigator.
	• Hospitalization may be indicated.
	
	** In cases of anaphylaxis, epinephrine should be usedimmediately.
	Participant is permanently discontinued from further study drugtreatment.
		No subsequent dosing

IV/iv = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events;NSAID = nonsteroidal anti-inflammatory drugs; po = oral.

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v5 at http://ctep.cancer.gov

18.2 Appendix B Procedures for Participants Exhibiting Immune-Related Adverse Events

Adverse events of a potential immunologic etiology, or irAEs, may be defined as AEs of unknown etiology, associated with drug exposure and consistent with an immune phenomenon. Immune-related AEs may be predicted based on the nature of the compounds, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes before labeling an AE as an irAE.

Recommendations for management of specific immune-mediated AEs known to be associated with other PD-1 inhibitors (e.g., pembrolizumab, nivolumab) are detailed in Appendix B Table (below). Algorithms for evaluation of selected immune toxicities that have previously been attributed to PD-1 inhibitors and management guidelines for irAEs not detailed elsewhere in the Protocol should follow the ASCO or ESMO Clinical Practice Guidelines (Brahmer et al 2018, Haanen et al 2017).

Table 1. Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events

General Instructions:
1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where XmAb23104 has been withheld, they can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv5)	Action Taken with XmAb23104	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs andsymptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiatecorticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2	Monitor participants for signs andsymptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs

	Grade 3	Withhold XmAb23104	mg/kg prednisone or equivalent) followed by taper	and ileus). Participants with Grade ≥ 2 diarrhea suspecting colitis shouldconsider GI consultation and performing endoscopy to rule outcolitis. Participants with diarrhea/colitis should be advised to drink liberalquantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation without elevated bilirubin or Increased bilirubin alone	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4, or /findings consistent with DILI (Grade 2 AST/ALT and total bilirubin > 2 × ULN)	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Immune-related AEs	**Toxicity Grade or Conditions (CTCAEv5)**	**Action Taken with XmAb23104**	**irAE Management with Corticosteroid and/or Other Therapies**	**Monitor and Follow-up**
AST / ALT elevation with bilirubin >1.5 × ULN (unless Gilbert's syndrome)	Grade > 1	Permanently discontinue	Administer corticosteroids (initial dose of 2 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests(consider weekly or more frequently until liver enzyme value returned to baseline or is stable)

T1DM or Hyperglycemia	Newly onset T1DMor Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs andsymptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptomsof hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptomsof thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptomsof thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent)	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

			followed by taper.	
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or excludeother causes
	Grade 3 or 4	Permanently discontinue		

Immune-related AEs	**Toxicity Grade orConditions (CTCAEv5)**	**Action Taken with XmAb23104**	**irAE Management with Corticosteroid and/or Other Therapies**	**Monitor and Follow-up**
All other immune-related AEs	Intolerable/ persistentGrade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or excludeother causes
	Grade 3	Withhold or discontinue based onthe type of event. Events that require discontinuation include and not limited to: Guillain-Barré Syndrome, encephalitis		
	Grade 4 or recurrentGrade 3	Permanently discontinue		

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; DILI = drug-induced liver injury; irAE = immune-related adverse event;IV = intravenous; T1DM = type 1 diabetes mellitus; ULN = upper limit of normal.
[1] Withhold or permanently discontinue XmAb23104 is at the discretion of the investigator or treating physician.
***NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of XmAb23104 is required, the drugs may be resumed when AE resolves to Grade ≤ 2 and is controlled with hormonal replacementtherapy or achieved metabolic control (in case of T1DM).*