MD Anderson IND Sponsor Cover Sheet

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Protocol Title	Clinical Study to Assess Efficacy and Safety of MDA-TIL (Autologous Expanded Tumor Infiltrating Lymphocytes) across Multiple Tumor Types
Protocol Phase	2
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Clinical Study to Assess Efficacy and Safety of MDA-TIL (Autologous Expanded Tumor Infiltrating Lymphocytes) across Multiple Tumor Types

MD Anderson Study Number: 2017-0671

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Version: 2.1

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LIST OF ABBREVIATIONS

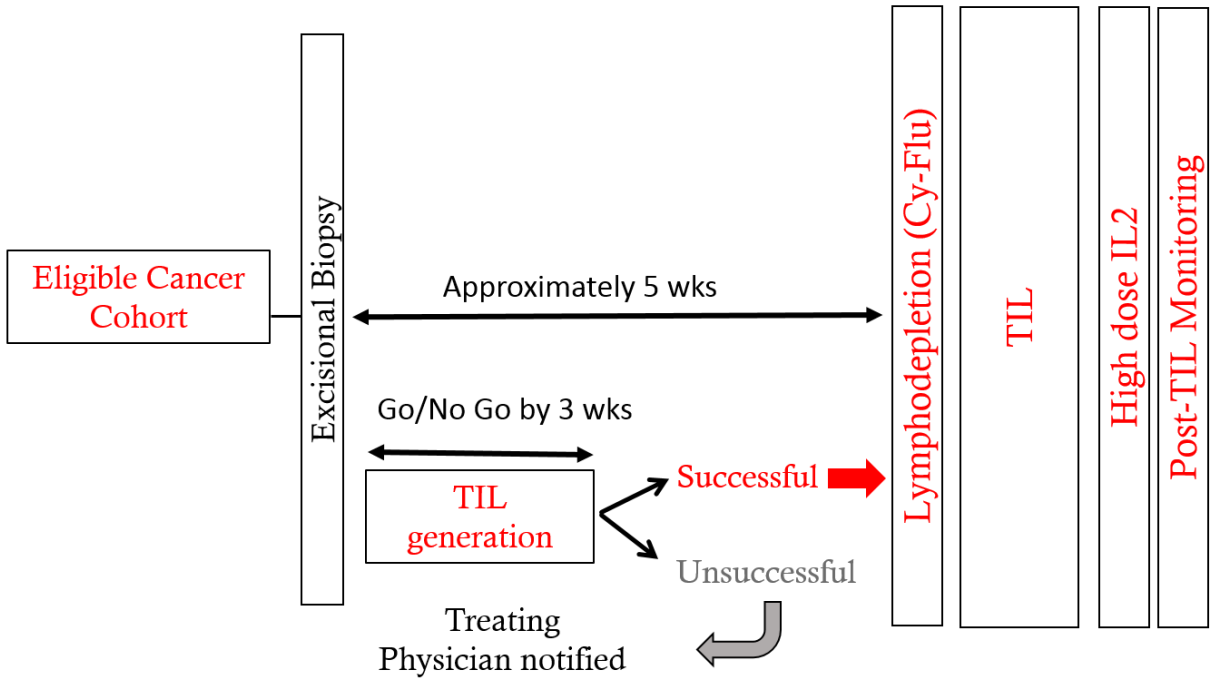
ACT	Adoptive Cell Therapy
AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase
ASMR	Age-standardized Mortality Rate
aPTT	Activated Partial Thromboplastin Time
BID	Twice Per Day
BSA	Body Surface Area
CBC	Complete Blood Count
CD4+T	CD4+ T Cells
CD8+T	CD8+ T Cells
CFR	Code of Federal Regulations
CI	Confidence Interval
CLS	Capillary Leak Syndrome
CMO	Contract Manufacturing Organization
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CrCl	Creatinine Clearance
CT	Computed Tomography
CTCAE v4.03	Common Terminology Criteria for Adverse Events Version 4.03
D5W	Dextrose 5% by weight
DCR	Disease control rate
DOR	Duration of Response
EBV	Epstein-Barr Virus
ECHO	Echocardiogram
EKG	Electrocardiogram
EOC	Epithelial Ovarian Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire - Core 30 instrument
EWV	Early Withdrawal Visit
FDA	Food and Drug Administration
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HRQoL	Health-related Quality-of-life
ICH	International Conference on Harmonization
IL	Interleukin
IND	Investigational New Drug (Application)
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IRB	Institutional Review Board
IUD	Intrauterine Device
IV	Intravenous
IVPB	Intravenous Piggyback
LVEF	Left Ventricular Ejection Fraction

M1	HLA-DR+CD68+ M1 Macrophages
M2	CD163+ or CD204+ M2 Macrophages
MDA-TIL	Autologous Tumor Infiltrating Lymphocytes
MDACC	MD Anderson Cancer Center
MRI	Magnetic Resonance Imaging
MUGA	Multiple Gated Acquisition Scan
NCI	National Cancer Institute
Neu	CD66b+ Neutrophils
NMA	Nonmyeloablative
NS	Normal Saline
OC	Ovarian Cancer
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PDAC	Pancreatic Ductal Adenocarcinoma
PE	Physical Exam
PET	Positron Emission Tomography
PFS	Progression-free survival
PHI	Personal Health Information
PI	Principal Investigator
PJP	Pneumonitis Jiroveci Pneumonia
PO	Per Os (by mouth)
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
QTcF	Fridericia's Corrected QT Interval
RECIST	Response Evaluation Criteria in Solid Tumors
REP	Rapid Expansion Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SGOT	Serum Glutamic-oxaloacetic Transaminase
SGPT	Serum Glutamic-pyruvic Transaminase
SMX	Sulfamethoxazole
TCR	T-cell Receptor
TIL	Tumor-infiltrating lymphocyte
TMA	Tissue Microarray
TMP	Trimethoprim
Treg	FOXP3+ Regulatory T Cells
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior written agreement as specified in the Strategic Alliance Agreement and/or the Study Order pertinent to this study, and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

SCHEMATIC OF STUDY DESIGN



1. INTRODUCTION

1.1 BACKGROUND INFORMATION

Adoptive cell immunotherapy (ACT) using tumor-infiltrating lymphocytes (TIL) consists of isolation of TIL from fresh tumor biopsy, interleukin (IL)-2 mediated selection of activated cells expressing IL-2 receptors, and expansion to large numbers *ex-vivo* with subsequent administration of the expanded TIL product to the patient. TIL infusion is preceded by lymphodepletion chemotherapy to reduce the number of regulatory T cells, creating a hostile tumor microenvironment, and followed by adjuvant IL-2 to assist with *in vivo* engraftment. As with other immunotherapy approaches, TIL therapy has been most extensively utilized in melanoma where response rates of approximately 50% have been reported (Dudley et al., 2002; Dudley et al., 2005; Dudley et al., 2008; Radvanyi et al., 2012).

Previous trials investigating TIL therapy in other solid tumors have shown limited success, however most of these studies predated the recognition of the crucial importance of lymphodepleting chemotherapy prior to TIL infusion (Aoki et al., 1991; Freedman et al., 1994; Fujita et al., 1995; Ikarashi et al., 1994).

However, when ovarian cancer TIL therapy was administered after surgical extirpation and primary adjuvant chemotherapy (a situation analogous to the use of lymphodepleting chemotherapy), the results, in small numbers of patients, showed 100% three-year survival in patients who received TIL versus 67.5% in those who did not (Fujita et al., 1995). More recently, clinical activity for TIL therapy has been reported for other solid tumors (Stevanovic et al., 2015; Tran et al., 2014) and clinical testing for other epithelial malignancies including ovarian cancer (OC), renal cell carcinoma, colorectal cancer, pancreatic cancer, hepatocellular carcinoma, cholangiocarcinoma and gastric cancer is ongoing at NCI (ClinicalTrials.gov identifier NCT02482090, NCT02926053, NCT01883297, NCT01174121).

1.2 SCIENTIFIC RATIONALE

1.2.1 INCLUSION OF COLORECTAL CARCINOMAS

Non-resectable metastatic CRC is incurable with life expectancy of approximately 2 years. Frontline therapy is highly active with response rates over 50%, however subsequent therapy, 2nd line and greater have response rates <15% with short time to progression and novel therapeutic approaches in the 2nd line or greater and urgently needed. There is substantial evidence that tumor-infiltrating lymphocytes possess important predictive and prognostic significance in colorectal cancer (Cavalleri et al., 2019; Kong et al., 2019; Reissfelder et al., 2015; Zhou et al., 2019). In addition, T cells recognizing shared antigens have been isolated from TIL and peripheral T cell populations from patients with colorectal cancers (Cafri et al., 2019; Lo et al., 2019).

Direct evidence for TIL recognition of colorectal tumor specific antigens has been reported by Rosenberg's Group at NCI (Tran et al., 2016; Turcotte et al., 2014). Germane to this trial, they identified a polyclonal CD8+ T-cell response against mutant KRAS G12D in tumor-infiltrating lymphocytes obtained from a patient with metastatic colorectal cancer. TIL therapy resulted in objective regression of all metastases. Interestingly, progression of one the lesions 9 months after therapy was associated with the loss of chromosome 6 encoding the relevant class I major histocompatibility complex (MHC) molecule resulting in tumor immune evasion (Tran et al., 2016). In addition, Rosenberg's group has successfully identified TP53 specific TCRs from the TIL analysis pipeline in 12 patients, of which 9 are colorectal cancer, again demonstrating the potential of endogenous TIL therapy in CRC (NCI Workshop on Cell-based Immunotherapy for Solid Tumors held December 10-11, 2018 in Bethesda, Maryland).

Our group has had an active interest in evaluating TIL expansion from CRC patients undergoing resection of liver metastasis and have collected over 40 cases with successful TIL expansion rate utilizing 41BB stimulation of 83%.

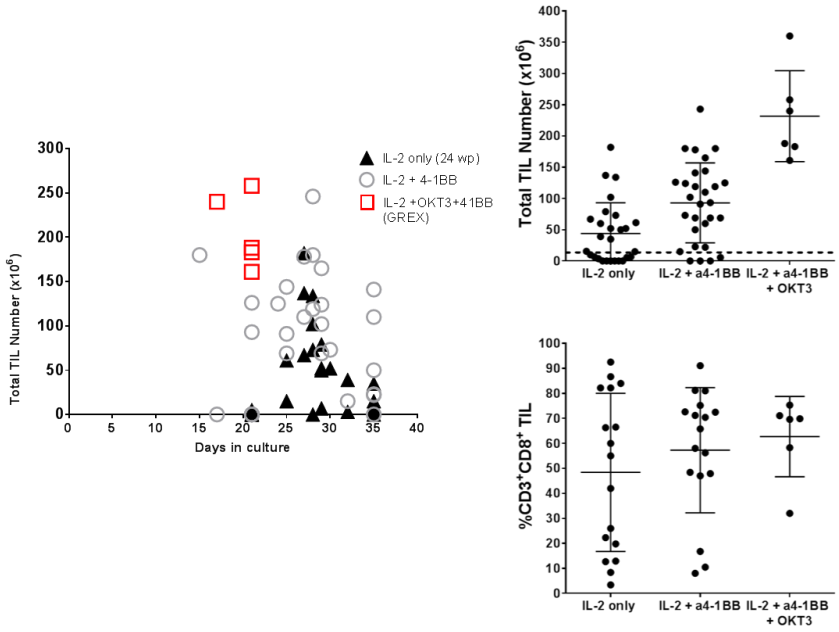


Figure 1: TIL expansion from colorectal carcinoma patient tumor sample. High yield of TIL can be expanded with the use of anti-4-1BB (BMS, Urelumab), anti-CD3 (clone OKT3) and IL-2 and the resulting product is enriched in $CD3^+CD8^+$ T cells.

1.2.2 INCLUSION OF CHEMORESISTANT EPITHELIAL OVARIAN CANCER

Despite high rates of complete response to the combination of tumor reductive surgery and adjuvant platinum-taxane based chemotherapy, the vast majority of patients with stage III/IV epithelial ovarian cancer (EOC) recur with a median progression free survival of approximately 18 months (Jayson, Kohn, Kitchener, & Ledermann, 2014). With rare exceptions, relapsed ovarian cancer is considered incurable, and patients who progress on, or recur less than 6 months from the completion of platinum-based chemotherapy, are deemed "platinum resistant," and constitute a very poor prognostic group. Despite decades of clinical investigations, most therapies are associated with only modest response rates and a typical median progression free survival of 3-4 months across a wide variety of cytotoxic and biological agents (Naumann & Coleman, 2011). Thus, development of new strategies that will ultimately improve the overall survival of patients with EOC represents a crucial unmet need.

Immunogenicity of EOC has been well documented, and there is extensive literature demonstrating the presence of clonally activated $CD3^+CD8^+$ $TCR\alpha\beta^+$ T-cells in ovarian tumors and their prognostic significance (Hayashi et al., 1999; Ioannides, Freedman, Platsoucas, Rashed, & Kim, 1991; Peoples, Schoof, Andrews, Goedegebuure, & Eberlein, 1993; Preston et al., 2013; Sato et al., 2005; Webb, Milne, Watson, Deleeuw, & Nelson, 2014; Zhang et al., 2003). TIL derived from EOC patients demonstrate tumor specificity and killing of autologous EOC tumor cells (Ioannides et al., 1991). A meta-analysis of studies investigating the prognostic significance of TIL in ovarian cancer revealed an independent positive effect on survival associated with the presence of TIL (Hwang, Adams, Tahirovic, Hagemann, & Coukos, 2012). Emerging data on single agent, anti-PD1 / antiPDL-1 therapies in ovarian cancer point to response rates of only 10-15%. These low response rates could be improved by using adoptive cell

therapy (ACT) strategies and as noted in **Section 1.1** clinical trials aimed at testing the efficacy of TIL therapy in ovarian cancer are ongoing.

Our group has characterized the immune component of OC, explored the ability to grow and expand TIL from tumor fragments, and tested their functionality (Sakellariou-Thompson et al., SITC 2015). Extensive flow cytometry analysis detected a robust, activated T-cell infiltrate that can be grown from OC samples obtained pre- and post-chemotherapy. The addition of an agonistic anti-41BB antibody to the cultures preferentially increased $CD8^+$ TIL outgrowth as well as favored the expansion of Natural Killer cells. Importantly, success rate of TIL growth was increased from 40% to 90% for cultures grown without and with anti-41BB respectively. Next, it was established that the $CD3^+$ TIL initially grown with anti-41BB could be rapidly expanded at least 1000-fold over two weeks. Finally, the rapidly expanded T cells exhibited anti-tumor capabilities in the context of re-directed killing assays (Sakellariou-Thompson et al., SITC 2015).

1.2.3 INCLUSION OF SUBJECTS WITH PANCREATIC CANCER

Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease and has been identified as a "recalcitrant cancer" by the National Cancer Institute (NCI). Despite being the 12th most common cancer in 2017, with 53,670 new cases, it is the 3rd deadliest in the U.S. with 43,090 deaths, having surpassed breast cancer deaths last year. The 5-year survival rate for patients with stage IV, or metastatic, disease is a dismal 1%. While the age-standardized mortality rate (ASMR) for breast cancer and colorectal cancers have decreased by over 50% during the past 30 years and are decreasing annually by 2.4% and 2.7% respectively, the ASMR for PDAC has only improved marginally (Rahib et al., 2014). Thus, it is estimated that PDAC will be the second leading cause of cancer death in North America within 10 years. Late presentation of the disease, no screening methods, lack of effective treatments, and high mortality rates highlight the desperate need for development of innovative methods to treat this disease.

Currently there are only six FDA approved agents for PDAC and at present, front-line therapy for metastatic PDAC is combination chemotherapy, most commonly FOLFIRINOX (fluorouracil, irinotecan, and oxaliplatin) or gemcitabine and nanoparticle albumin-bound paclitaxel. We have not made a seismic shift in the overall survival for this disease over the past few decades. Given our growing understanding of the biology and tumor microenvironment and lack of actionable genomic aberrations, it is crucial to exploit therapeutic efforts outside of cytotoxics and targeted agents and evaluate benefit of T cell therapies in PDAC.

The tumor microenvironment is composed by multiple cell types, molecular factors, and extracellular matrix forming a strong desmoplastic reaction, which is a hallmark of the disease. A complex cross-talk between tumor cells and the stroma exists with reciprocal influence that dictates tumor progression and ultimately the clinical outcome. In this context, tumor infiltrating immune cells through secretion of chemokine and cytokines exert an important regulatory role. TILs, mast cells, and macrophages all contribute to a Th2-type inflammatory and immunosuppressive microenvironment. Fibrosis is due to activation by tumor and immune cells of pancreatic stellate cells, which are responsible for extracellular matrix deposition. Importantly, fibrogenesis is differentially regulated by Th1 (i.e., IFN-γ) and Th2 (i.e., IL-4, IL-5, and IL-13) cytokines, which exert opposing roles by promoting collagen degradation and synthesis, respectively (Wynn, 2004). Th1 or Th2 polarized immune cells may thus differentially contribute to fibrosis in PDAC and possibly influence tumor progression.

Studies have shown that tumor-infiltrating $CD4^{+}T^{high}/CD8^{+}T^{high}/\%Treg^{low}$ and $\%M1^{high}/M2^{low}$ are independent prognosticators useful for evaluating the immune microenvironment of PDAC. In a study by Ino and colleagues, using immunohistochemistry, they examined tumor-infiltrating $CD68^{+}$ pan-macrophages, $HLA\text{-}DR^{+}CD68^{+}$ M1 macrophages (M1), $CD163^{+}$ or $CD204^{+}$ M2 macrophages (M2), $CD66b^{+}$ neutrophils (Neu), $CD4^{+}$ T cells ($CD4^{+}$T), $CD8^{+}$ T cells ($CD8^{+}$T), and $FOXP3^{+}CD4^{+}$ regulatory T cells (T_{reg}) in 212 cases of PDAC, and conducted correlation and survival analyses using the Kaplan–Meier method and Cox proportional hazards model (Ino et al., 2013). Higher levels of tumor-infiltrating pan-macrophages, M2, Neu, or the ratio of Tregs to $CD4^{+}$T (%Treg) are significantly associated with shorter survival, whereas higher levels of tumor-infiltrating $CD4^{+}$T, $CD8^{+}$T, or the ratio of M1 to pan-macrophages (%M1) are significantly associated with longer survival (Ino et al., 2013).

Several groups have optimized methods for generating pancreatic cancer–specific TILs that can be used for adoptive cellular therapy of patients with pancreatic cancer including our team at MDACC.

1.2.3.14-1BB AGONIST TREATMENT FACILITATES TIL EXPANSION FROM POORLY IMMUNOGENIC TUMORS; THE CASE OF PANCREATIC CANCER.

Our group at MDACC piloted pre-clinical development of TIL therapy for pancreatic cancer and observed a significantly lower TIL infiltration in fresh PDAC samples compared to melanoma, coupled with a predominance of $CD4^{+}$ T cells (**Figure 2**). The poor $CD8^{+}$ T cell infiltrate observed may not be sufficient to respond to immunomodulatory drugs administered systemically (i.e.it is a cold tumor). Indeed, pancreatic cancer has been resistant to single agent checkpoint blockade (Brahmer et al., 2012; Royal et al., 2010); TIL therapy could provide these patients with large numbers of pancreatic-cancer specific T cells, potentially turning a “cold tumor” into a “hot tumor.”

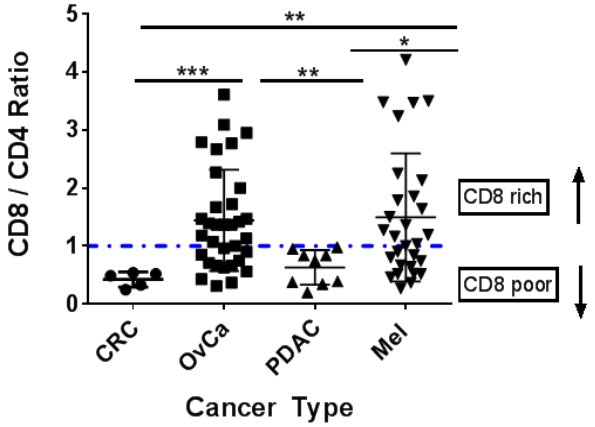


Figure 2. PDAC tumors are poor in CD8+ T cells.
Freshly dissociated tumor tissue of different tumor types were evaluated for the presence of T cells by flow cytometry. The percentage of CD4 and CD8 T cells within the CD3+ T cell population was evaluated and a ratio of %CD8/%CD4 was determined.

1.2.3.2 TIL CAN BE EXPANDED FROM PDAC SAMPLES AND THEIR EXPANSION IS POTENTIATED WITH ANTI-4-1BB ANTIBODY

In our hands the success rate of growing TIL from PDAC samples increased from 25% to 50% with the addition of 4-1BB antibody to the cultures. Importantly, the amount of tissue used to generate TIL was **no larger than 2 core biopsies,** which is critical given the limited availability of tissue from pancreatic cancer patients. The threshold for considering a culture successful was established at $12x10^6$ TIL grown from 6 tumor fragments within 5 weeks based on a scale-down from our melanoma clinical protocol. Use of anti-4-1BB also dramatically increased the proportion of $CD8^+$ TIL in the product (**Figure 3**).

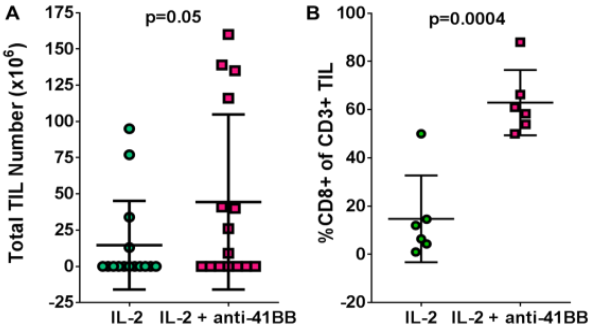


Figure 3. Addition of anti-4-1BB increases the total number of TIL and the percentage of CD8+ TIL grown from PDAC tumors.

PDAC tumor fragments were cultured with IL-2 alone (green circles) or with IL-2 plus anti-4-1BB (pink squares). (A) Total number of TIL (B) % CD8 in the product. N=16. Statistical analysis was done using a Mann-Whitney t test.

1.3 POTENTIAL RISKS AND BENEFITS

1.3.1 KNOWN POTENTIAL RISKS AND THEIR MITIGATION

Adoptive cell therapy with TIL is comprised of four main components each of which carry potential risks.

1. **Tissue acquisition.** Culture and expansion of TIL requires surgical biopsies of primary or metastatic tumor sites (metastatic only for PDAC). As with any surgical procedure and depending on the patients' other comorbidities, surgical biopsies have well-known risks including bleeding, infection, delayed wound healing, and damage to surrounding structures. In addition, there may be risks associated with general anesthesia. Overall, life-threatening complications are quite rare, and risks are minimized at MDACC by use of collaborating expert surgeons who specialize in oncologic surgery.
2. **Non-myeloablative lymphodepleting chemotherapy consisting of cyclophosphamide and fludarabine.** The regimen of cyclophosphamide (60 mg/kg IV days -7 and -6) and fludarabine (25 mg/m^2 days -5 to -1) used in this trial is a standard aspect of TIL and some other ACT protocols and has been used in hundreds of patients in and outside of clinical trials. Therefore, the major risks of this regimen are well characterized and include: hemorrhagic cystitis from cyclophosphamide (mitigated by co-administration of Mesna), neutropenia and lymphopenia and their infectious complications (mitigated by the use of antimicrobial, antiviral, and anti-fungal therapeutic and prophylactic antibiotics).
3. **TIL infusion.** Early toxicities related specifically to the infusion of the cells (those which are seen immediately following the cell infusion and prior to IL-2 administration) are generally mild and include fevers, chills, headache, and malaise. Toxicities that occur following administration of IL-2 but are thought to be related to the cells include immune-mediated events. In metastatic melanoma patients, autoimmune toxicities include vitiligo, transient uveitis, hearing loss, and

vestibular dysfunction. However, these side effects are thought to be related to melanocyte specificity and have not been reported in cervical cancer patients treated with TIL therapy (Stevanovic et al., 2015).

4. **IL-2.** IL-2 administration has been associated with capillary leak syndrome (CLS), which is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. CLS results in hypotension and reduced organ perfusion, which may be severe and can result in death. CLS may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes.

IL-2 treatment is associated also with impaired neutrophil function (reduced chemotaxis) and with an increased risk of disseminated infection, including sepsis and bacterial endocarditis. Consequently, preexisting bacterial infections should be adequately treated prior to initiation of IL-2 therapy. Patients with indwelling central lines are particularly at risk for infection with gram positive microorganisms. Antibiotic prophylaxis with oxacillin, nafcillin, ciprofloxacin, or vancomycin has been associated with a reduced incidence of staphylococcal infections. IL-2 administration should be withheld in patients developing moderate to severe lethargy or somnolence; continued administration may result in coma.

The standard approach to the administration of IL-2 is to continue dosing until grade 3 or 4 events occur but this study calls for 1 to 6 doses based on tolerance. The most commonly seen grade 4 events are pulmonary and renal impairment and mental status changes. These toxicities may sometimes require intubation for protection of the patient's airway. It is important to note that although these patients require significant supportive measures during this period, almost all toxicities are reversible, and the overwhelming majority of patients have suffered no long-term sequelae following this treatment regimen. However, fatal complications are possible.

1.3.2 KNOWN POTENTIAL BENEFITS

Most of the evidence for efficacy of ACT using TIL is in patients with metastatic melanoma where this therapy has been most often used. Response rates of approximately 50% have been reported (Dudley et al., 2002; Dudley et al., 2005; Dudley et al., 2008) at NCI and also at MDACC (Radvanyi et al., 2012). Approximately 20-24% durable complete response (CR) rates have been observed with TIL therapy (Goff JCO 2016). However, more recently TIL therapy has been reported to result in complete durable responses of at least 54 and 46 months or partial responses in patients with non-melanoma cancers including cervical cancer (Stevanovic et al., 2015; Stevanovic et al., 2017) and cholangiocarcinoma (Tran et al., 2014). In both cervical cancer and cholangiocarcinoma, responses were observed in subjects for whom conventional therapies would have been extremely unlikely to produce a response. The two subjects with cervical cancer who achieved complete remission had already received multiple lines of chemotherapy and radiotherapy and would receive the recommendation for best supportive care with transition to hospice by most clinicians had they not elected to undergo TIL therapy at NCI.

Hence, the potential benefit for subjects on this trial is response that is durable in nature.

2. OBJECTIVES

2.1 PRIMARY

The primary objective of this investigation is to evaluate efficacy using objective response rate (ORR) according to RECIST v1.1 in subjects with ovarian cancer, PDAC, and colorectal cancers.

2.2 SECONDARY

The secondary objectives of this investigation are to:

1. Determine the disease control rate (DCR) within and across cohorts,
2. Determine the duration of response (DOR),
3. Determine progression-free survival (PFS) and overall survival (OS), and
4. Further characterize the safety profile of adoptive cell therapy with TIL across multiple tumor types.

2.3 EXPLORATORY

The exploratory objectives of this investigation are to:

1. Establish duration of TIL persistence,
2. Compare the molecular and immunological features of tumors before and after TIL therapy,
3. Prospectively evaluate the existing immunotherapy response criteria (irRECIST) as the best response assessment tool for TIL therapy among a diverse group of solid tumors,
4. Investigate TIL attributes (CD8 %, CD27 and CD28 expression) and correlation with response to therapy,
5. Assess tumor marker (CA19-9; CA-125) response in patients who produce this tumor marker, and
6. Assess Health-Related Quality of Life (HRQOL).

3. STUDY DESIGN AND ENDPOINTS

This is a multi-cohort phase II trial aimed at evaluating the efficacy of MDA-TIL in subjects with: a) advanced or relapsed colorectal cancers refractory to conventional therapy, b) platinum-resistant ovarian cancer, and c) PDAC who have progressed on, or received maximal benefit from, front-line therapy. Each cohort begins with ten subjects in the first stage, and expansion to the second stage is guided by a modified Simon's two stage design as described in the Statistical Considerations section.

3.1 PRIMARY ENDPOINT

The primary endpoint is ORR by RECIST v1.1 for ovarian cancer, colorectal cancer, and PDAC.

3.2 SECONDARY ENDPOINTS

The secondary efficacy endpoints include CRR, DCR, DOR, PFS using RECIST v1.1, and OS. The landmark survival rates will also be estimated for 6 and 12 months. DCR includes complete response (CR), partial response (PR), and stable disease (SD). Safety endpoints will include overall assessment of AEs including grade 3 or greater non-hematological toxicities, SAEs and treatment-emergent AEs by grade and relationship to the study treatment.

3.3 EXPLORATORY ENDPOINTS

Exploratory endpoints will include the following:

1. Duration of TIL persistence as determined by T cell receptor (TCR) sequencing of infused T cells serially isolated following MDA-TIL infusion, or alternatively iRepertoire assessment of mRNA for the TCRs.
2. Response as determined by the immune-related response criteria (Wolchok et al., 2009).
3. Immunological Phenotype of MDA-TIL at the time of infusion by multichannel flow cytometry
4. Baseline and post-treatment tumor assessment via IHC, TCR sequencing, and transcriptional analysis.
5. HRQOL as assessed per EORTC QLQ-C30 questionnaire.

4. ELIGIBILITY CRITERIA

4.1 PARTICIPANT INCLUSION CRITERIA

4.1.1 GENERAL INCLUSION CRITERIA

1. Age between 18 and 70
2. Subjects must be willing and able to provide informed consent.
3. Clinical performance status of ECOG 0 or 1 at enrollment and within 7 days of initiating lymphodepleting chemotherapy.
4. Subjects must have an area of tumor amenable to excisional biopsy (core biopsies may be allowed as detailed in section 6.1.20) for the generation of TIL separate from, and in addition to, a target lesion to be used for response assessment.
5. Any prior therapy directed at the malignant tumor, including radiation therapy, chemotherapy, and biologic/targeted agents must be discontinued at least 28 days prior to tumor resection for preparing TIL therapy.
6. Within 7 days of enrollment, subjects must meet the following laboratory criteria:
   - Absolute neutrophil count (ANC) $\geq 1000/mm^3$
   - Hemoglobin ≥ 9.0 g/dL (transfusion allowed)
   - Platelet count $\geq 100{,}000/mm^3$
   - ALT/SGPT and AST/SGOT < 2.5 x the upper limit of normal (ULN)
     - Patients with liver metastases may have LFT ≤ 5.0 x ULN
   - Calculated creatinine clearance (Cockcroft-Gault) ≥ 50.0 mL/min
   - Total bilirubin ≤ 1.5 X ULN
   - Prothrombin Time (PT) & Activated Partial Thromboplastin Time (aPTT) ≤ 1.5 X ULN (correction with vitamin K allowed) unless subject is receiving anticoagulant therapy (which should be managed according to institutional norms prior to and after excisional biopsy)
   - Negative serum pregnancy test (female subjects of childbearing potential)
7. Subjects must not have a confirmed human immunodeficiency virus (HIV) infection.
8. Subjects must have a 12-lead electrocardiogram (EKG) showing no active ischemia and Fridericia's corrected QT interval (QTcF) less than 480 ms.
9. Subjects must also have a negative dobutamine stress echocardiogram before beginning treatment.

10. Subjects of childbearing potential must be willing to practice an approved highly effective method of birth control starting at the time of informed consent and for 1 year after the completion of the lymphodepletion regimen.
    Approved methods of birth control are as follows:
    - Hormonal contraception (i.e. birth control pills, injection, implant, transdermal patch, vaginal ring),
    - Intrauterine device (IUD),
    - Tubal Ligation or hysterectomy,
    - Subject/partner status post vasectomy,
    - Implantable or injectable contraceptives, and
    - Condoms plus spermicide
11. Able to adhere to the study visit schedule and other protocol requirements.
12. Pulmonary function tests (spirometry) demonstrating forced expiratory value (FEV) 1 greater than 65% predicted or forced vital capacity (FVC) greater than 65% of predicted.

4.1.2 COHORT-SPECIFIC INCLUSION CRITERIA

In addition to meeting the above general inclusion criteria subjects must also meet respective cohort specific inclusion criteria listed below.

Ovarian Cancer

1. Subjects must have high grade non-mucinous histology (carcinosarcomas are allowed).
2. Subjects must have failed at least two prior lines of chemotherapy (i.e. frontline adjuvant chemotherapy plus one additional line for recurrent/progressive disease), or have platinum resistant disease.

Colorectal Cancer

1. Subjects with colorectal adenocarcinoma must have metastatic disease that is considered incurable with currently available therapies and have derived maximal benefit from or have become refractory to frontline conventional therapy (e.g. FOLFOX, FOLFIRI).
2. Subjects should have low disease burden such that in the treating physician's opinion the patient would not require additional intervening treatment for 7-8 weeks (required for TIL harvest and manufacturing).

Pancreatic Adenocarcinoma

1. Subjects must have histologically or cytologically documented diagnosis of PDAC with oligo-metastatic disease.
2. Subjects must have progressed on, or received maximal benefit from, front-line therapy.
3. Patients may have received unlimited lines of prior standard of care therapy.
4. Patients with ascites or carcinomatosis are not eligible for the study.
5. Patients will need an albumin of ≥ 3.0 mg/dL within 7 days of enrollment.

4.2 PARTICIPANT EXCLUSION CRITERIA

4.2.1 GENERAL STUDY EXCLUSION CRITERIA

1. Active systemic infections requiring intravenous antibiotics, coagulation disorders or other major medical illnesses of the cardiovascular, respiratory or immune system. PI or his/her designee shall make the final determination regarding appropriateness of enrollment.
2. Patients with active viral hepatitis.
3. Patients who have a left ventricular ejection fraction (LVEF) < 45% at Screening.
4. Patients with a history of prior adoptive cell therapies.
5. Persistent prior therapy-related toxicities greater than Grade 2 according to Common Toxicity Criteria for Adverse Events (CTCAE) v4.03, except for peripheral neuropathy, alopecia, or vitiligo prior to enrollment.
6. Primary immunodeficiency.
7. History of organ or hematopoietic stem cell transplant.
8. Chronic steroid therapy, however prednisone or its equivalent is allowed at < 10 mg/day.
9. Patients who are pregnant or nursing.
10. Presence of a significant psychiatric disease, which in the opinion of the principal investigator or his/her designee, would prevent adequate informed consent.
11. History of clinically significant autoimmune disease including active, known, or suspected autoimmune disease. Subjects with resolved side effects from prior checkpoint inhibitor therapy, vitiligo, psoriasis, type 1 diabetes or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded.
12. History of clinically significant chronic obstructive pulmonary disease (COPD), asthma, or other chronic lung disease.
13. History of a second malignancy (diagnosed in the last 5 years). Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
14. History of known active central nervous system metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to initiation of lymphodepletion.
15. Has received a live vaccine within 30 days prior to the initiation of lymphodepletion.
16. Patients who have a contraindication to or history of hypersensitivity reaction to any components or excipients of the TIL therapy or the other study drugs: NMA-LD (cyclophosphamide, mesna, and fludarabine); IL-2; Any component of the TIL infusion product formulation including human serum albumin (HSA), IL-2, and dextran-40.
17. Any other condition that in the investigator's judgement would significantly increase the risks of participation.

4.3 TREATMENT ELIGIBILITY CRITERIA

After tissue acquisition, subjects must also meet treatment eligibility criteria before beginning lymphodepletion.

4.3.1 TREATMENT INCLUSION CRITERION

Within 24 h of starting lymphodepleting chemotherapy, subjects must meet the following laboratory criteria:

- Absolute neutrophil count (ANC) ≥ 1000/mm^3
- Hemoglobin ≥ 9.0 g/dL (transfusion allowed)
- Platelet count ≥ 100,000/mm^3
- ALT/SGPT and AST/SGOT ≤ 2.5 x the upper limit of normal (ULN)
  - Patients with liver metastases may have liver function tests (LFT) ≤ 5.0 x ULN
- Calculated creatinine clearance (Cockcroft-Gault) ≥ 50.0 mL/min
- Total bilirubin ≤ 1.5 X ULN

4.3.2 TREATMENT EXCLUSION CRITERIA

- Patient has any complication or delayed healing from excisional procedure that in the investigator's opinion would increase the risks of lymphodepletion, adoptive TIL therapy and adjuvant IL-2.
- Patients has a decline in performance status to ECOG > 1 (at the visit prior to admission for lymphodepletion).

4.4 COMPLETION OR DISCONTINUATION OF TREATMENT

4.4.1 TREATMENT COMPLETION

Completion of treatment is defined as having received any volume of MDA-TIL infusion followed by at least 1 dose of adjuvant IL-2.

4.4.2 CRITERIA FOR EARLY DISCONTINUATION FROM TREATMENT

This study includes a one-time treatment regimen consisting of lymphodepleting chemotherapy, MDA-TIL infusion, and adjuvant IL-2 (up to 6 doses). Discontinuation from study treatment should be considered if any of the following criteria are met. However, unless the patient also meets criteria for discontinuation from study participation, every effort should be made to continue follow-up and assessment of all patients, including those that do not complete the full course of therapy, as specified in the schedule of events.

Criteria for early discontinuation from treatment are:

- Grade 3 or greater autoimmunity that involves vital organs (heart, kidneys, brain, eye, liver, colon, adrenal gland, lungs) with symptoms emerging following MDA-TIL infusion,

- Grade 3 or greater allergic reaction including bronchospasm or generalized urticaria that does not resolve after medical management in the opinion of the Investigator,
- Grade 3 or greater toxicity due to IL-2 that does not decrease to Grade 2 or less within 96 hours of management,
- Determination by the Investigator that continued treatment is not in the best interest of the patient,
- Withdrawal by patient. The patient (or parents/legal guardian for patients < 18 years of age) may withdraw consent to treatment but continue consent for follow-up evaluations and/or survival status,
- Pregnancy,
- Patient meets criteria for early discontinuation from study, and
- Patient has become ineligible for study after tumor harvest and prior to MDA-TIL or IL-2 administration

4.4.3 CRITERIA FOR EARLY DISCONTINUATION FROM STUDY

- Withdrawal by patient. The patient (or parents/legal guardian for patients < 18 years of age) may withdraw consent. All efforts should be made to continue consent for survival status follow-up.
- Patient has become ineligible for study after tumor harvest or did not receive any study treatment.
- Death.
- Lost to follow-up after 3 documented attempts to contact the patient.

4.4.4 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Some subjects may undergo tumor harvest and TIL manufacture but will not receive the infusion of investigational product. If MDA-TIL is not administered to the patient for whatever reason, even if after lymphodepleting chemotherapy, then the patient should remain on study, but data collection will be reduced to survival status and start of any new anticancer therapy for 3 years. Such subjects will be considered unevaluable for statistical analysis of efficacy and will be replaced.

If a patient must initiate anti-cancer therapy or exhibits disease progression after TIL infusion they will remain in the study, but the data collection will be reduced to response status, survival status and other anti-cancer therapy for 3 years.

5. STUDY AGENTS

5.1 STUDY AGENTS AND THEIR ACQUISITION

5.1.1 LYMPHODEPLETION REGIMEN

The lymphodepletion regimen is scheduled to start on Day -7, after notification from the MDACC Cell Therapy Lab that TIL production is expected to be successful for the patient. Patients may receive lymphodepleting chemotherapy as inpatient or outpatient at the discretion of the investigator. Modification of the lymphodepletion regimen is allowed as clinically indicated and should be guided by daily hematological parameters as described below for fludarabine in heavily pre-treated patients or subjects with a history of prolonged myeloid recovery. The regimen comprises 2 daily doses of cyclophosphamide (with mesna) followed by 5 daily doses of fludarabine and should be administered as per institutional protocol/standards for nonmyeloablative chemotherapy. Guidelines for preparation and

administration are described below. Subjects should be dosed using actual body weight but not to exceed 140% of Ideal Body Weight as defined below:

- **Ideal Body Weight for Males** = 50 kg + 2.3 x (number of inches over 60 inches in height)

Example: ideal body weight of a 5'10'' male subject
50 + 2.3 x 10 = 73 kg

- **Ideal Body Weight for Females** = 45.5 kg + 2.3 (number of inches over 60 inches in height)

Example: ideal body weight of a 5'3'' female subject
45.5 + 2.3 x 3 = 52.4 kg

Drugs required for lymphodepletion including cyclophosphamide, fludarabine, and mesna will be obtained from the MD Anderson Investigational Pharmacy. Supportive medications including antimicrobials will be obtained through MD Anderson clinical pharmacy. For formulation and packaging of the lymphodepletion regimen please refer to respective package inserts for cyclophosphamide, fludarabine, and mesna.

Variations from the lymphodepletion (e.g. infusion times; schedule of treatments, etc.) prior to day 0 will be documented in the medical record but will not be considered protocol violations/deviations.

5.1.1.1 CYCLOPHOSPHAMIDE

Cyclophosphamide will be administered at 60 mg/kg/day intravenously (IV) in normal saline (NS) over approximately 2 hours on Days -7 and -6. Mesna 60 mg/kg with dextrose 5% by weight (D5W) or NS infused intravenously over 24 h on Days -7 and -6.

As noted above the dose will be based on the patient's actual body weight, but to prevent undue toxicity, it will not exceed the dose based on 140% of the maximum ideal body weight (defined above). For patients with a history of multiple lines of prior cytotoxic chemotherapy, history of radiation, or prolonged neutropenia with prior chemotherapy, the dose of cyclophosamide may be reduced to 30 mg/kg with approval of the PI.

5.1.1.2 FLUDARABINE

Fludarabine will then be infused at 25 mg/m^2 IV piggyback (PB) daily over approximately 15-30 minutes on Days -5 to -1. To prevent undue toxicity with fludarabine, the dose will be based on body surface area (BSA), but will not exceed a dose calculated on surface areas based on body weights greater than 140% of the maximum ideal body weight.

Fludarabine dose will be adjusted according to estimated creatinine clearance (CrCl) as follows:

CrCl 50-79 mL/min: Reduce dose to 20 mg/m^2

CrCl 40-49 mL/min: Reduce dose to 15 mg/m^2

Hematological parameters (complete blood count [CBC] and differential) are to be reviewed daily during lymphodepletion. If the absolute lymphocyte count falls below 100 cells/mm^3 at any point during lymphodepletion, the remaining dose(s) of fludarabine may be omitted following discussion with the PI. If lymphodepletion is terminated early, TIL infusion may be initiated at least 24 hours after the last dose of fludarabine if absolute lymphocyte count remains below 100 cells/mm^3.

5.1.2 MDA-TIL (AUTOLOGOUS EXPANDED TIL PRODUCT)

The TIL product used in this protocol is a cellular investigational product comprising a live cell suspension of autologous TIL derived from the patient's own tumor. Each dose contains up to 150 x 10^9 total viable lymphocytes. The total volume to be infused will be up to 600 mL dependent on total cell dose. TIL will be manufactured in a state-of-the-art GMP facility that will allow compliance with all FDA regulations regarding investigational cell transfer products. The MD Anderson TIL facility has demonstrated the ability to successfully expand TIL on the tumor samples attempted and have successfully treated over 100 patients with melanoma and other cancers with TIL therapy.

Urelumab (anti-41BB) will be provided by BMS for use only in the MDA-TIL production. Urelumab will not be administered to patients. This reagent will be supplied at volumes of 1.6 or 3 mL in a 5-mL vial at a concentration of 5 mg/mL. The Urelumab will be stored at 2-8 °C and will be protected from light and freezing.

The procedures and reagents for expanding the human TIL cells and the Certificates of Analysis are contained in the Chemistry, Manufacturing, and Controls document (CMC) located in the IND office.

At least 24 hours from the last dose of fludarabine, MDA-TIL is administered via intravenous infusion by gravity at a rate of 5-10 mL/min and not over more than 3 hours.

If not already hospitalized for the lymphodepleting chemotherapy, the patient will be admitted 1-2 days prior to planned MDA-TIL administration and prepared with overnight intravenous hydration prior to the MDA-TIL administration. Patients will remain hospitalized until the completion of the IL-2 therapy, as per institutional standards.

Patients must be premedicated with acetaminophen/paracetamol 650 mg by mouth (PO) and diphenhydramine (or other histamine H1 antagonist) 25 to 50 mg IV or PO between 30 and 60 minutes prior to administration of LN-145. Additional supportive therapy may include indomethacin (50 to 75 mg q6h), ranitidine (150 mg q12h), and meperidine (25 to 50 mg) IV for severe rigors/chills.

Severe infusion reactions have been reported during adoptive cell transfer. Thus, appropriate emergency medications (e.g., epinephrine and diphenhydramine) will be available at bedside during administration and institutional guidelines will be followed for administering supportive care for anaphylaxis and other infusion reactions. Patients should not be premedicated with corticosteroids to prophylax against such reactions without prior clearance from the PI or Co-PI. Corticosteroids may be used only at the discretion of the treating physician for Grade 4 reactions or if the patient is not responsive to other medications.

For subjects who experience an NCI CTCAE v 4.03 grade 1 or 2 infusion reaction, MDA-TIL infusion may be resumed if the event is short-lived and responds to supportive therapies such as acetaminophen and histamine blockers. Patients who experience grade 3 or 4 infusion reactions may not resume treatment. Although clinical presentations can be overlapping, when possible, efforts should be undertaken to differentiate hypersensitivity type infusion reactions (due to excipients in MDA-TIL) from cytokine release syndrome based on clinical and laboratory evaluation since the latter can be mitigated using tocilizumab and other cytokine directed therapies.

5.1.3 INTERLEUKIN 2

The IL-2 infusion will begin 3-24 h after completion of the MDA-TIL infusion. IL-2 will be administered at a dose of 600,000 IU/kg (based on total body weight) and will be administered by IV infusion at a

frequency of every 8-12 hours as per institutional standard of care and continued for up to a maximum of six doses or as tolerated. IL-2 doses will be skipped if patient experiences a Grade 3 or 4 toxicity due to IL-2 except for reversible Grade 3 toxicities common to IL-2 such as diarrhea, nausea, vomiting, hypotension, skin changes, anorexia, mucositis, dysphagia, or constitutional symptoms and laboratory changes. Management of IL-2 toxicity is detailed in **Appendix A**. If these toxicities can be easily reversed within 24 hours by supportive measures, then additional doses may be given. If greater than 2 doses of IL-2 are skipped, IL-2 administration will be stopped. In addition, dosing may be held or stopped at the discretion of the treating Investigator.

Refer to the current IL-2/aldesleukin (Proleukin®) package insert for additional information. IL-2 will be obtained through the MD Anderson Investigational Pharmacy.

6. STUDY PROCEDURES AND SCHEDULE

6.1 STUDY SPECIFIC PROCEDURES

Potentially eligible patients will be approached by their clinical teams at MDACC. Study procedures are summarized in the **Schedule of Events (Section 6.2)**.

6.1.1 INFORMED CONSENT

Potential subjects will be informed about the study by the investigator. The risks, benefits, and alternatives will be discussed and the Informed Consent Document will be signed before any study related assessments are performed.

6.1.2 ELIGIBILITY CRITERIA

Subjects must meet all inclusion criteria and must not have any of the conditions specified in the exclusion criteria (as described in **Section 4**). Confirmation of general, cohort, specific, and treatment inclusion/exclusion criteria must be documented within seven days of starting lymphodepletion chemotherapy.

6.1.3 DEMOGRAPHIC DATA

The demographic data will include date of birth (as allowed per local regulations), age, gender, and race/ethnic origin.

6.1.4 MEDICAL HISTORY

Relevant and significant medical/surgical history and concurrent illnesses will be collected for all patients at Screening (Visit 1) and updated as applicable. Any worsening from pre-existing conditions should be reported as AEs. Patient's prior anti-cancer treatment will also be collected.

6.1.5 CONFIRMATION OF DIAGNOSIS

Documentation of cohort-specific diagnosis of cancer must be made and confirmed histologically.

6.1.6 CONCOMITANT MEDICATIONS

All medications and therapies (prescription, and non-prescription, including herbal supplements) taken by the patient up to 28 days prior to Screening (Visit 1) will be collected in the medical record, including the stop dates for medications prohibited in the study, at the time of consent. All medications and therapies being taken by the patients, or changes thereof, at any time during the study, will be recorded in the medical record (see **Section 6.3**).

6.1.7 BASELINE TOXICITY ASSESSMENT

All baseline grade 2 and higher toxicities will be assessed as per CTCAE v4.03. Any events occurred after screening, but prior to enrollment/tumor resection, will be recorded as Medical History in the database, unless the events are related to protocol mandated procedures. Any events occurring after enrollment/tumor resection will be captured as AEs in the database until the 6 Month visit, subject is taken off the study, or starts other cancer therapy.

6.1.8 VITAL SIGNS

Vital signs shall include height, weight, pulse, respirations, blood pressure and temperature. Height will be measured at Screening (Visit 1) only. All other vital signs will be measured at applicable time points.

On Day 0 (Visit 11/MDA-TIL infusion), vital signs will be monitored per MD Anderson melanoma TIL infusion unit protocol unless otherwise clinically indicated, for up to approximately 24 hours post MDA-TIL infusion.

6.1.9 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

An ECOG performance status will be assessed at Screening (Visit 1) and other time points indicated on the schedule of events.

6.1.10 PHYSICAL EXAMINATION

Physical examination will be conducted for all visits except for Tumor Resection and shall include vital signs and weight, head and neck, cardiovascular, pulmonary, extremities, and other relevant evaluation. Exams during conducted during follow-up will be symptom directed. Clinically significant changes in the exam findings will be recorded as adverse events as indicated.

6.1.11 SAFETY BLOOD AND URINE TESTS

Safety blood and urine tests will be collected and analyzed locally at every visit as indicated in the Schedule of Events (**Section 6.2**).

6.1.12 HUMAN LEUKOCYTE ANTIGEN (HLA) TYPING

Sample collection for high resolution HLA Class I typing will be conducted according to the Schedule of Events (**Table 1**).

6.1.13 INFECTIOUS DISEASE SEROLOGY

Serology for the following diseases will be completed at Screening (Visit 1) to be analyzed locally per institutional standard: HIV, Hepatitis B Virus, Hepatitis C Virus, Cytomegalovirus (CMV), Herpes Simplex Virus; Epstein-Barr virus (EBV) (may be within previous 3 months to Tumor Resection/Visit 2), Chagas Disease, Human T cell Lymphotropic Virus, and West Nile Virus. Sickle Cell Disease will also be screened. Additional testing is to be done as clinically indicated.

6.1.14 ESTIMATED CREATININE CLEARANCE

The creatinine clearance will be calculated by site using the Cockcroft-Gault formula at Screening only.

6.1.15 CARDIAC EVALUATION

All subjects must have a baseline 12-lead EKG and assessment of ventricular function by echocardiogram or MUGA. In addition, subjects must have a negative dobutamine stress echocardiogram at Screening.

6.1.16 PULMONARY FUNCTION TESTS

Pulmonary evaluation will be completed within 28 days from Screening (Visit 1). Prior evaluations completed within 6 months prior to Screening (Visit 1) will be accepted. An FEV1 greater than 65% of predicted or FVC greater than 65% of predicted is required.

Patients who are unable to conduct reliable PFT spirometry measurements due to abnormal upper airway anatomy (e.g. tracheostomy) may undergo a 6-minute walk test to be evaluate pulmonary function. These patients must walk a distance of at least 80% predicted for age and sex as well as maintain oxygen saturation greater than 90% throughout.

6.1.17 COLONOSCOPY

Colonoscopy is only required for patients who have had a documented Grade 2 or greater diarrhea or colitis due to previous immunotherapy within six months of Screening. Patients that have been asymptomatic for at least 6 months from Screening or had a normal colonoscopy post anti-PD-1/anti-PD-L1 treatment, with uninflamed mucosa by visual assessment will not need to repeat the colonoscopy.

6.1.18 HRQOL QUESTIONNAIRE – EORTC QLQ-C30

Health related quality of life (HRQOL) questionnaire will be conducted in person at baseline Day -21 (Visit 3) and be performed as the first procedure on the subsequent visits. See the Schedules of Events (**Section 6.2**) for specific time points. Only patients who are fluent in English will participate in the questionnaires. Failure to complete any questionnaires will not be considered a deviation requiring reporting.

6.1.19 RADIOGRAPHIC ASSESSMENTS

Radiographic assessments by computed tomography (CT) scans with contrast of the chest, abdomen and pelvis are required for all patients for tumor assessments. CT scans are performed as indicated in the Schedule of Events until progressive disease by modified RECIST v1.1 is noted (or if the patient withdraws full consent). Response assessments should be evaluated and documented by a qualified radiologist participating in the trial.

Magnetic Resonance Imaging (MRI) or positron emission tomography (PET) scans of the chest, abdomen and pelvis in lieu of CT scans may be allowed for patients who have an intolerability to contrast media. The same method of assessment (CT or MRI) and the same technique for acquisition of data should be used consistently throughout the study to characterize each identified and reported lesion.

Radiographic assessments will occur at screening, baseline, and then at 6, 12, 18, and 24 weeks post MDA-TIL infusion. Thereafter, patients will be evaluated for response approximately every 12 weeks through month 24 or until their participation on the study ends. Additional radiological assessments may be performed as clinically indicated.

6.1.20 TUMOR RESECTION / EXCISIONAL BIOPSY

Prior to surgical biopsy, subject eligibility will be confirmed, and the PI or designee will provide approval for patient enrollment into the clinical trial and subsequent tumor resection. Subjects will undergo a pre-procedural consultation and a separate informed consent by the team performing the surgical biopsy per institutional standards. The tumor resection should be done as a research procedure. However, if a routine procedure is already medically required, the tumor resection may be done as part of that procedure.

Ideally, the targeted tumor should have not been previously irradiated. If the tumor has been previously irradiated a minimum period of 3 months must have elapsed between irradiation and resection, during which time additional target-tumor growth must have been demonstrated. If enrolled, tumor resection is expected to occur approximately 6 weeks prior to the anticipated MDA-TIL infusion (Day 0).

The PI, in consultation with treating physician(s) and Interventional Radiology faculty, will have the discretion to determine that it would be in the subject's best interest to undergo multiple core biopsies for tumor harvest rather than open surgery. This judgment will be based on patient safety and surgical risk considerations, as well as, the feasibility of obtaining sufficient tissue from Interventional Radiology-performed multiple core biopsies for tumor harvest. This decision will be communicated to, and approved by, the TIL manufacturing team.

MDA-TIL is an autologous investigational product which is procured and delivered by means that have more in common with autologous blood product delivery than those of traditional drug production. It is imperative that only the patient's own (autologous) study treatment (MDA-TIL) be administered to the same individual patient. For these reasons, the patient specimen must be procured and handled per a strict protocol to ensure optimal quality of the specimen and minimum transport time to and from the processing MDACC Cell Therapy Lab facility, as well as to ensure the appropriate identification of the study product at all times including infusion back into the patient.

Refer to the CMC for details.

6.1.21 ADDITIONAL RESEARCH BIOPSY

In cases where additional or excess tumor tissue can be safely procured at the time of the initial excisional biopsy for TIL harvest, excess tumor tissue for research will be sent to Dr. Chantale Bernatchez's laboratory according to established institutional procedures. Provision of adequate amount of tumor tissue for TIL manufacturing is priority over the collection of additional tumor tissue that is sent for research. Every effort should be made to obtain adequate tumor tissue for both TIL manufacturing and additional analysis.

In addition, a mandatory on-study biopsy will be used to ascertain molecular and immunological changes following treatment and as well as to document presence of infused T cells in the tumor. The tumor tissue analysis will include: 1) immunohistochemical studies to identify individual immune cell populations and immune marker expression including tissue mass cytometry (if sufficient tissue available) and 2) DNA and RNA analysis, including possible exploratory genomic and transcriptomic evaluation and TCR sequencing to evaluate infused TIL homing to tumor (in the post-treatment biopsy).

Provision of adequate amount of tumor tissue for TIL manufacturing is priority over the collection of additional tumor tissue for research. Every effort should be made to obtain adequate tumor tissue for both TIL manufacturing and additional analysis.

Additionally, if a diagnostic biopsy is required while a patient is on study, including during the follow-up period to confirm disease progression, additional tissue may be taken for research as an optional procedure.

6.1.22 BIOLOGICAL AND IMMUNE MONITORING

Up to 500 x 10^6 TIL from the infusion product (and genetic material extracted from these samples) will be stored for research. Flow cytometry analysis of the infused TIL will be done in Dr. Bernatchez's laboratory, and DNA from the infusion product will be sent for TCR sequencing. The samples in these research studies will be used to gain further information about the disease and the characteristics of the TIL before and after infusion.

Peripheral blood will be collected from the patients and processed into 3 fractions: whole blood, serum, and plasma. These fractions will be used for biological monitoring, immune monitoring, and T cell tracking using TCR sequencing. Blood samples will be drawn at the time points listed in the Schedules of Events (Tables 2 and 3).

6.2 SCHEDULES OF EVENTS

Table 1. Schedule of Events: Pre-treatment and Treatment Phases

	Pre-treatment Phase			Treatment Phase								
Visit Number	**1**	**2**	**3**	**4**	**5**	**6, 7, 8, 9, 10**	**11**	**12, 13, 14, 15**	**16**	**17**	**18**	**19**
Visit Name	**Screening[a]**	**Biopsy**	**Baseline (Day -14 to -21)**	**Day -7**	**Day -6**	**Days -5, -4, -3, -2, -1**	**Day 0 (MDA-TIL Infusion)**	**Days 1, 2, 3, 4**	**Day 14**	**Day 28**	**Day 42 (Week 6)**	**Day 84 (Week 12)**
Visit Window (in days)	≤28	-7[b]	N/A	N/A	N/A	N/A	N/A	N/A	± 7	± 7	± 7	± 7
Written Informed Consent[c]	X											
Medical History[d]	X											
Documentation of diagnosis	X											
Physical Exam[e]	X		X	X	X	X	X	X	X	X	X	X
Vital Signs[f]	X	X	X	X	X	X	X[g]	X	X	X	X	X
ECOG performance status	X	X	X	X			X			X	X	X
CBC and Chemistry Panel[h]	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation tests[i]	X	X		X								
Thyroid tests[j]	X											X
Urinalysis[k]	X			X	X	X	X	X	X	X	X	X
ß-HCG Serum Pregnancy Test[l]	X		X	X								
Infection testing[m]	X											
HLA typing[n]	X											
Cardiac Evaluations[o]	X											
Pulmonary function tests[p]	X											
Colonoscopy[q]	X											
Tumor Assessments (CT/MRI)[r]	X		X[s]								X	X
Tumor Markers[t]			X								X	X
Response Assessments											X	X
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[u]	X	X	X	X	X	X	X	X	X	X	X	X
Tumor Excision		X[v,w]									X[w]	
NMA lymphodepletion[x]				X	X	X						
MDA-TIL Infusion[y]							X					
IL-2[z]								X				
Immune Monitoring[aa]		X		X					X	X	X	X
HRQOL Questionnaire[bb]			X									X
Prophylactic Medications[cc]												
Infection Prevention[dd]				Administered daily until ANC ≥500/mm^3								
PJP[ee]				X	X	X	X	X	X	X	X	X
Filgrastim[ff]								X				
Fungal Prophylaxis[gg]							X	X	X	X	X	X

Herpes Virus Prophylaxis[hh]							X	X	X	X	X	X

[a] All screening criteria must be assessed within 28 days of the biopsy (Visit 2)
[b] Assessment of ECOG, Concomitant Meds, and Adverse Events, as well as blood draws (for CBC, Chemistry Panel, Coagulation tests, and Immune Monitoring) may be done up to 5 days before the tumor excision if the patient has a pre-operative consultation during that time.
[c] Also includes assignment of subject identification number
[d] Including Demographics and history of tobacco and alcohol use. (History of tobacco and alcohol use can be collected at any time.)
[e] Physical examination (PE) will include gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, and throat, respiratory system, skin, psychiatric (mental status), general nutrition. See **Section 6.1.10**.
[f] Vital signs will include height, weight, heart rate, respiratory rate, blood pressure, and temperature. Height will be measured at Screening only. BSA and BMI will be calculated at Day -7 (Visit 4) only. See **Section 6.1.8**.
[g] On Day 0 (MDA-TIL infusion), vital signs will be monitored every 30 minutes during infusion then hourly (+/-15 minutes) for four hours and then routinely (every four to six hours), unless otherwise clinically indicated, for up to approximately 24 hours post TIL infusion.
[h] Chemistry: sodium, potassium, chloride, total CO2, or bicarbonate, creatinine, glucose, BUN, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, direct bilirubin, LDH, total protein, total CK, and uric acid. Hematology: CBC with differential.
[i] PT, PTT, and INR on the marked Visits and as clinically indicated.
[j] Thyroid panel (to include TSH and Free T3 and T4) on the marked Visits and as clinically indicated.
[k] Bilirubin, Blood, Glucose, Ketones, pH, Protein, Specific gravity, Color and Appearance.
[l] Only in women of childbearing potential
[m] See **Section 6.1.13**.
[n] See **Section 6.1.12**. Blood for HLA typing can be drawn any time before Day 0.
[o] See **Section 6.1.15**.
[p] Pulmonary evaluation using spirometry will be completed for all patients. See **Section 6.1.16**.
[q] Colonoscopy is only required for documented Grade 2 or greater diarrhea or colitis as a result of previous immunotherapy within six months from Screening. Patients that have been asymptomatic for at least 6 months from Screening or had a normal colonoscopy post anti-PD-1/anti-PD-L1 treatment, with uninflamed mucosa by visual assessment will not need to repeat the colonoscopy. See **Section 6.1.17**.
[r] CT Scans of the chest, abdomen, and pelvis are required at the indicated time points. Additional radiological assessments may be performed per Investigator's discretion. MRI may be used if patients are intolerable to contrast media. See **Section 6.1.19**.
[s] Baseline scans must occur prior to lymphodepletion.
[t] CA19-9 for patients with PDAC and CA-125 for patients with ovarian cancer.
[u] Any AEs occurred after Screening but prior to enrollment/tumor resection will be recorded as Medical History in the database. Any AEs occurred after enrollment/tumor resection will be captured as AEs through Day 168 (Visit 21/Month 6) and as clinically indicated, or until the first dose of the subsequent anti-cancer therapy, whichever occurs first. All AEs attributed to protocol-required procedures or treatment will be collected through Day 672 (Visit 25/Month 24). See **Section 7**.

[v] For tumor harvest for TIL manufacturing and FFPE tumor slides for exploratory analyses, see **Section 6.1.20**. The disease will also be reassessed after the tumor excision.
[w] For research. See **Section 6.1.21**.
[x] Cyclophosphamide with mesna for 2 days at Day -7 and Day -6 (Visits 4 thru 5) followed by 5 days of fludarabine at Day -5 thru Day -1 (Visits 6 thru 10). See **Section 5**.
[y] MDA-TIL infusion is to be done 1 to 2 days after the last dose of agent in the NMA lymphodepletion regimen. See **Section 5**.
[z] Initiate IL-2 at 600,000 IU/kg within approximately 3 to 24 hours after MDA-TIL infusion and continue every 8-12 hours for up to six doses. See **Section 5**.
[aa] Blood draw for Immune Monitoring is to be collected at Tumor Resection (Visit 2), Day -7 (Visit 4), Day 14 (Visit 16) through Day 84 (Visit 19/Week 12), and Day 168 (Visit 21/Month 6) through Day 336 (Visit 23/Month 12) and ETV. See **Section 6.1.22**.
[bb] HRQOL Questionnaire(s) to include EORTC QLQ-C30 version 3.0 is to be performed as the first procedure at baseline Day -21 (Visit 3) and be performed as the first procedure on Day 84 (Visit 19/Week 12), Day 168 (Visit 21/Month 6), Day 336 (Visit 23/Month 12), and Day 672 (Visit 25/Month 24).
[cc] See **Section 6.3.3** for details regarding prophylactic medications.
[dd] See **Section 6.3.3.1** for details regarding infection prevention.
[ee] Pneumocystis Jiroveci Pneumonia (PJP) prophylaxis should be given as described in **Section 6.3.3.2**.
[ff] Filgrastim should be administered daily as described in **Section 6.3.4.1.**
[gg] Fungal prophylaxis should be administered each day described in **Section 6.3.3.4**.
[hh] Herpes prophylaxis should be administered as described in **Section 6.3.3.3**.

Table 2. Schedule of Events: Post-treatment and Long-term Follow-up

	Post-treatment Follow-up							**Long-term Follow-up**
Visit Number	**20**	**21**	**22**	**23**	**24**	**25**	**EWV**	
Visit Name	**Day 126 (Month 4.5/ Week 18)**	**Day 168 (Month 6)**	**Day 252 (Month 9)**	**Day 336 (Month 12)**	**Day 504 (Month 18)**	**Day 672 (Month 24)**	**Early Withdrawal Visit**	**Quarterly Contact**
Visit Window (in days)	± 14	± 14	± 14	± 14	± 21	± 21		± 21
Physical Exam[a]	X	X	X	X	X	X	X	
Vital Signs[b]	X	X	X	X			X	
ECOG performance status	X	X	X	X	X	X	X	
CBC and Chemistry Panel[c]	X	X					X	
Coagulation tests[d]	As Clinically Indicated							
Thyroid tests[e]	As Clinically Indicated							
Urinalysis[f]	X	X	X	X	X	X	X	
Tumor Assessments (CT/MRI)[g]	X	X	X	X	X	X	X	
Tumor Markers[h]	X	X	X	X	X	X	X	
Response Assessments	X	X	X	X	X	X	X	
Concomitant Meds	X	X	X	X			X	
Adverse events[i]	X	X					X	
Immune Monitoring[j]		X	X	X			X	
HRQOL Questionnaire[k]		X		X		X		
Survival Follow-up[l]								X
Prophylactic Medications[m]								
Infection Prevention[n]	Administered daily until ANC ≥500/mm^3							
PJP[o]	X	X						
Fungal Prophylaxis[p]	X	X						
Herpes Virus Prophylaxis[q]	X	X						

[a] PE will include gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, and throat, respiratory system, skin, psychiatric (mental status), general nutrition. PE conducted during follow-up will be symptom directed. See **Section 6.1.10**.
[b] Vital signs will include weight, heart rate, respiratory rate, blood pressure, and temperature.
[c] Chemistry: sodium, potassium, chloride, total CO2, or bicarbonate, creatinine, glucose, BUN, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, direct bilirubin, LDH, total protein, total CK, and uric acid. Hematology: CBC with differential.
[d] PT, PTT, and INR as clinically indicated.
[e] Thyroid panel (to include TSH and Free T3 and T4) as clinically indicated.
[f] Bilirubin, Blood, Glucose, Ketones, pH, Protein, Specific gravity, Color and Appearance.
[g] CT Scans of the chest, abdomen and pelvis, are required at the indicated time points. Additional radiological assessments may be performed per Investigator's discretion. MRI may be used if patients are intolerable to contrast media. See **Section 6.1.19**.
[h] CA19-9 for patients with PDAC and CA-125 for patients with ovarian cancer.
[i] Any AEs occurred after Screening, but prior to enrollment/tumor resection, will be recorded as Medical History in the database. Any AEs occurred after enrollment/tumor resection will be captured as AEs through Day 168 (Visit 21/Month 6) and as clinically indicated, or until the first dose of the subsequent anti-cancer therapy, whichever occurs first. All AEs attributed to protocol-required procedures or treatment will be collected through Day 672 (Visit 25/Month 24). See **Section 7**.
[j] Blood draw for Immune Monitoring is to be collected at visits between Day 168 (Visit 21/Month 6) through Day 336 (Visit 23/Month 12) and ETV. See **Section 6.1.22**.
[k] HRQOL Questionnaire(s) to include EORTC QLQ-C30 version 3.0 is to be performed as the first procedure at baseline Day -21 (Visit 3) and be performed as the first procedure on Day 84 (Visit 19/Week 12), Day 168 (Visit 21/Month 6), Day 336 (Visit 23/Month 12), and Day 672 (Visit 25/Month 24).
[l] Patients are to be contacted quarterly (~every 3 months) once discontinue/complete the Post-Treatment Follow-up to assess disease status and subsequent anticancer therapy.
[m] See **Section 6.3.3** for details regarding prophylactic medications.
[n] See **Section 6.3.3.1** for details regarding infection prevention.
[o] PJP prophylaxis should be given as described in **Section 6.3.3.2**.
[p] Fungal prophylaxis should be administered each day described in **Section 6.3.3.4**.
[q] See **Section 6.3.3.3**.

6.3 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

Concomitant medications and any changes in them will be recorded in the medical record.

6.3.1 PERMITTED MEDICATIONS, TREATMENTS, AND PROCEDURES

Medications for medical problems other than antineoplastic agents are permitted. Those with conditions requiring anti-inflammatory drugs for chronic conditions potentially affecting TIL administration may be considered only with approval of the PI.

Palliative radiation therapy is permitted between tumor resection and lymphodepletion as long as it does not affect target and non-target lesions.

Use of systemic steroid therapy ≤ 10 mg/day of prednisone or equivalent is permitted. Use of > 10 mg/day of prednisone or equivalent is permitted in cases of exacerbation of known disease or for treatment of new symptoms on study per Investigator's discretion.

Any changes in concomitant medications will be recorded only in the patient's medical record throughout the trial.

For subject who have CT IV contrast allergy, radiologic evaluation using MRI or PET-CT (without intravenous contrast is the preferred management. Every attempt should be made to maintain consistency in imaging modality for each patient.

6.3.2 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

All other anti-neoplastic drugs and radiation (except for that described in Section 6.3.1) are prohibited. Subjects are also discouraged from using over-the-counter supplements and homeopathic products, especially those with purported anti-inflammatory properties, such as boswelia.

6.3.3 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Patients treated with lymphodepletion are subject to opportunistic infections and appropriate infectious agent prophylaxis is required. The prophylaxis regimens and duration listed below may be modified as clinically indicated in consultation with an Infectious Diseases specialist.

6.3.3.1 INFECTION PREVENTION

Patients will receive levofloxacin starting on Day 1 at 500 mg daily (or an equivalent antibiotic) until ANC recovers to greater than 500/mm^3 for two days.

6.3.3.2 PNEUMOCYSTIS JIROVECI PNEUMONIA (PJP) PROPHYLAXIS

Patients will receive the fixed combination of trimethoprim (TMP) and sulfamethoxazole (SMX) as double strength (DS) tablet [DS tabs = TMP 160 mg/tab and SMX 800 mg/tab] PO BID on two days per week. TMP/SMX-DS will be taken by patients beginning on Day -7 and continuing for a minimum of 6 months after lymphodepletion. For patients with sulfa allergies, Pentamidine will be given (once discharged from the hospital) 300 mg IV every 21 days for 6 months after lymphodepletion. If IV Pentamidine is not feasible after discharge, PCP prophylaxis can be substituted with oral antimicrobials such as Atovaquone as per standard of

care for 6 months after lymphodepletion. Patients will be given prophylactic antibiotics intravenously during high dose IL-2 therapy.

6.3.3.3 HERPES VIRUS PROPHYLAXIS

Starting on the day of TIL infusion (Day 0) subjects will be administered valacylcovir 500 mg PO daily if patient is able to take oral medications or acyclovir 5 mg/kg IVPB every 8 hours if patient needs intravenous medications, which is continued for 6 months (or at the discretion of the treating physician). Reversible renal insufficiency has been reported with IV administered acyclovir but not with oral acyclovir. Neurologic toxicity including delirium, tremors, coma, acute psychiatric disturbances, and abnormal electroencephalograms has been reported with higher doses of acyclovir. If symptoms occur, a dosage adjustment will be made or the drug be discontinued. Acyclovir will not be used concomitantly with other nucleoside analogs (e.g. ganciclovir), which interfere with DNA synthesis. In patients with renal disease, the dose is adjusted as per product labeling.

6.3.3.4 FUNGAL PROPHYLAXIS

Patients will begin Fluconazole 200 mg PO daily with the T cell infusion (Day 0) and continue for 6 months (or at the discretion of the treating physician).

6.3.4 SUPPORTIVE MEDICATIONS, TREATMENTS, AND PROCEDURES

Other supportive medications will include the following.

6.3.4.1 FILGRASTIM (G-CSF)

To reduce the duration of neutropenia following NMA lymphodepletion chemotherapy, filgrastim (G-CSF) will be given at 5 µg/kg/day daily subcutaneously until ANC > 500/mm^3 for at least 2 consecutive days. Approximate dosing to correspond to the 300 mcg or 480 mcg dosage forms is allowed.

6.3.4.2 ONDANSETRON HYDROCHLORIDE (ZOFRAN)

Ondansetron will be used to control nausea and vomiting during the chemotherapy preparative regimen. It can cause headache, dizziness, myalgias, drowsiness, malaise, and weakness. Less common side effects include chest pain, hypotension, pruritus, constipation and urinary retention. Consult the package insert for a complete list of side effects and specific dose instructions.

6.3.4.3 FUROSEMIDE (LASIX)

Furosemide will be used to enhance urine output during the chemotherapy preparative regimen with cyclophosphamide. Adverse effects include dizziness, vertigo, paresthesias, weakness, orthostatic hypotension, photosensitivity, rash and pruritus. Consult the package insert for a complete list of side effects and specific dose instructions.

6.3.4.4 EMPIRIC ANTIBIOTICS

Patients will start on broad-spectrum antibiotics, either a 3rd or 4th generation cephalosporin with adequate pseudomonas coverage as per local antibiogram or a quinolone for temperature ≥ 38.5^{o}C with an ANC less than 500/mm^3. Aminoglycosides should be avoided if possible. Infectious disease consultation will be obtained from all patients with unexplained fever or any infectious complications.

6.3.4.5BLOOD PRODUCT SUPPORT

Using daily CBC values as a guide, the patient will also receive platelets and packed red blood cells as needed. Attempts will be made to keep Hgb > 8.0 g/dL, and platelets > 20,000/mL guided by the clinical scenario. Leukocyte filters will be utilized for all blood and platelet transfusions to decrease sensitization to transfused WBC's and decrease the risk of CMV infection. Irradiated blood and blood products should be used.

7. ASSESSMENT OF SAFETY

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

7.1 SPECIFICATION OF SAFETY PARAMETERS

7.1.1 DEFINITION OF ADVERSE EVENTS

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6 (R1) defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's preexisting condition. An abnormal laboratory finding (including EKG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (i.e., occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

The term AE is used to include both serious and non-serious AEs.

The Principal Investigator or designee shall be responsible for reporting and tracking of all AEs in compliance with all Laws, verifying and providing source documentation, and assigning the attribution for all AEs, included any expedited safety reports.

It will be left to the Investigator's clinical judgment whether or not an AE is of sufficient severity to require the patient's removal from the study treatment. A patient may also voluntarily discontinue treatment due to what he or she perceives as an intolerable AE. This should be captured in the database. If the patient was permanently

removed from the study or investigational product due to an SAE, this information must be included in either the initial or follow-up SAE Report Form and in the database.

7.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- 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 that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

1. Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
2. All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 24 hours of knowledge of the event).
3. **All life-threatening or fatal events** that are unexpected and related to the study drug must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
4. Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
5. Serious adverse events will be captured from the time of informed consent until 6 months after the last dose of IL-2 or until the first dose of anti-cancer therapy, whichever occurs first, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
6. Additionally, any serious adverse events that occur after the 30-day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

If any patient should die while on the study, the Investigator will inform within 24 hours and report the cause of death as an SAE. The cause of death should be recorded in detail on the SAE Report Form. Disease progression itself is not an AE, but the clinical signs or symptoms leading to death should be reported as an SAE with an outcome of death.

Reporting to FDA:

Serious adverse events will be forwarded to the FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32, including Grade 3-5 infusion reactions and all unexpected SAEs that require expedited reporting.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

7.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems are defined as per 21 CFR 312.32(a): An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.2 INVESTIGATOR COMMUNICATIONS WITH IOVANCE BIOTHERAPEUTICS

Reports for SAEs and other events requiring reporting will be sent to Iovance at the same time they are sent to the FDA, in accordance with the Strategic Alliance between MD Anderson and Iovance Biotherapeutics. Additionally, reports will also be sent to Synteract, an Iovance associated clinical research organization (CRO). Reports will be sent to Iovance Biotherapeutics' designated mailbox: *iovancesafety@iovance.com* and *safetyfax@synteract.com*.

7.3 ASSESSMENT OF SAFETY PARAMETERS

7.3.1 ASSESSMENT OF SEVERITY

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the CTCAE v4.03. The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

- Grade 1 (mild): An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- Grade 2 (moderate): An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- Grade 3 (severe): An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
- Grade 4 (life threatening): An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc.).
- Grade 5 (fatal): Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in **Section 7.1.2**. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

7.3.2 ASSESSMENT OF RELATIONSHIP

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

1. Definite – The AE is clearly related to the study treatment
2. Probable – The AE is likely related to the study treatment
3. Possible – The AE may be related to the study treatment
4. Unlikely – The AE is doubtfully related to the study treatment
5. Unrelated – The AE is clearly NOT related to the study treatment

7.4 RECORDING AND REPORTING OF AES AND SAES

All non-hematologic AEs and SAEs will be recorded. Only clinically significant laboratory abnormalities will be reported as an AE or SAE. A laboratory abnormality is considered clinically significant if it: resulted in initiation of concomitant therapy for laboratory abnormality; resulted in change of study treatment due to laboratory abnormality; or resulted in hospitalization or prolongation of hospitalization due to a laboratory abnormality. All laboratory abnormalities otherwise are reported in the database as laboratory assessment done per protocol defined schedule of assessment.

7.4.1 STUDY RECORDING PERIOD AND FOLLOW-UP FOR AES AND SAES

AEs and SAEs will be recorded and reported from time of informed consent throughout the treatment phase. SAEs will recorded and reported during the follow-up period (6 months after the last dose of IL-2) or until the first dose of anti-cancer therapy, whichever comes first. Treatment of procedure-related (possible, probable, definitive) AEs/SAEs must be reported at any time while a subject is being followed for tumor assessments.

During the course of the study all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

The investigator is responsible for following all AEs and SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

7.4.2 FOLLOW-UP OF UNRESOLVED ADVERSE EVENTS

Any AEs that are unresolved at the subject's last visit in the treatment phase are followed up by the investigator for as long as medically indicated, but without further recording in the database. After 30 days, only subjects with ongoing investigational product-related AEs/SAEs will continue to be followed for safety. Iovance Biotherapeutics and the IND office retain the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

7.4.3 SAFETY DATA EXCHANGE

MD Anderson and Iovance Biotherapeutics will share information with each other of any findings that may impact the safety of a Study Drug as Study Drug safety may adversely affect the health and safety of any Study subject, influence the conduct of a Study, alter an IRB's approval to continue a Study, or affect the willingness of a Study subject to continue participation in the Study.

SAE terminology and severity grading will be based on the NCI CTCAE v 4.03 guidelines.

7.4.3.1 IOVANCE BIOTHERAPEUTICS

MD Anderson and Iovance Biotherapeutics will share information as described in the MD Anderson/Iovance Strategic Alliance Agreement.

7.4.3.2 BRISTOL-MYERS SQUIBB

MD Anderson, Iovance Biotherapeutics and BMS will share information as described in the Investigator-Initiated Research Agreement between MD Anderson, Iovance Biotherapeutics and BMS. BMS will receive a quarterly AE report from MD Anderson using MD Anderson's SAE Report Forms.

Reports for Bristol-Myers Squibb (BMS) will be sent to their designated mailbox:

MG-RD-GPVE-PHARMACOVIGILANCE@bms.com.

7.4.4 UNANTICIPATED PROBLEM REPORTING

Unexpected events must be reported to Iovance Biotherapeutics safety department by electronic mail to iovancesafety@iovance.com and *safetyfax@synteract.com* within 24 hours of knowledge of the event using the eSAE form.

7.4.5 SPECIAL SITUATION REPORTS

Special situation reports include reports of medication error, overdose, adverse events associated with product complaints, occupational exposure, and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal/investigational product while in the control of the health care provider, patient, or consumer.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal/investigational product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the patient in question).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal/investigational product.

Occupational exposure is defined as the exposure to a medicinal/investigational product as a result of one's professional or non-professional occupation.

All other special situation reports involving the study treatment must be reported to Iovance Biotherapeutics safety department and Synteract by electronic mail to: iovancesafety@iovance.com and *safetyfax@synteract.com* within 24 hours of becoming aware of the situation. Special situations involving concomitant medications do not need to be reported; however, any AE resulting from a special situation should be reported in the database.

7.4.6 REPORTING OF PREGNANCY

Any pregnancy that occurs while on the study through 12 months from the last dose of IL-2 or until the first dose of the next anti-cancer therapy, whichever occurs first, must be reported using the Pregnancy Report form within 24 hours of becoming aware of the pregnancy. The pregnancy itself is not considered an AE nor is an induced abortion to terminate a pregnancy without medical reasons. Any premature termination of pregnancy (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an AE or SAE. The underlying medical reason for this procedure should be recorded as the AE or SAE term. A spontaneous abortion is always considered to be an SAE and will be reported as described in Section.

The patient should receive appropriate monitoring and care until the conclusion of the pregnancy to determine the outcome and status of the patient and child. The outcome should be reported to Iovance Therapeutics using the Pregnancy Outcome form. Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the patient has completed the study treatment and post-treatment follow-up visits, must be promptly reported to the Sponsor or their representative.

The pregnancy must be followed up until discharge following delivery or premature termination to determine outcome and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the patient has completed the study and considered by the Investigator as possibly related to the investigational product, must be promptly reported to the Sponsor or their representative.

Pregnancies of female partners of male study participants exposed to study treatment must also be reported and relevant information should be submitted to the safety CRO using the Pregnancy and Pregnancy Outcome forms within 24 hours. Monitoring of the female partners should continue until the conclusion of the pregnancy.

7.5 STUDY HALTING RULES

The study may be stopped following review of the safety data by MDACC IND Office according to their normal procedures.

7.6 SAFETY OVERSIGHT

Safety oversight will be performed by the MDACC IND Office. See Section 8.5 for the study specific monitoring plan.

8. STATISTICAL CONSIDERATIONS

8.1 STATISTICAL AND ANALYTICAL PLANS

The planned statistical analysis is primarily based on use of descriptive methods unless mentioned otherwise. Continuous data will be summarized as number of patients with non-missing data, mean, SD, median, min and max values. Categorical data will be summarized as counts and their related percentages, where applicable. Estimation of the primary endpoint, ORR, will use 80% CIs by the Wilson score method. All other estimations will adopt the 2-sided 95% criteria. PFS and OS will be summarized using Kaplan-Meier estimates. For exploratory objectives, paired t-test will be used to examine the molecular and immunological features of tumors before and after TIL therapy. Pearson correlation coefficient and linear regression, when appropriate, will be used to quantify the relationship between phenotypic attributes (CD8 %, CD27 and CD28 expression, etc.) and response to therapy. Missing data will not be imputed unless defined in the statistical analysis plan. The inferential statistics may be calculated (e.g., p-values) for a descriptive purpose.

There is no formal statistical comparison among multiple disease cohorts. The study success criteria are ≥ 3 responders for each of the cohorts at the end of Stage II.

8.2 ANALYSIS DATASETS

8.2.1 EFFICACY PRIMARY

The All-Treated analysis set consists of patients who had tumor harvested successfully and treated with nonmyeloablative chemotherapy, and MDA-TIL followed by IL-2 (at least 1 dose), based on the Investigators' assessment. Patients who are clinically/unequivocally progressed or expired prior to reaching the first radiological assessment will be included.

8.2.2 EFFICACY SECONDARY

The Efficacy-Evaluable analysis set consists of patients in the All-Treated analysis set who had an adequate baseline and at least one post-baseline radiological assessments by investigators.

8.2.3 SAFETY PRIMARY

The Safety analysis set consists of patients who had tumor harvested successfully and received at least one component of the study treatment; cyclophosphamide, fludarabine, MDA-TIL, or IL-2.

8.2.4 SAFETY SECONDARY

The Non-Treated analysis set consists of patients who have tumor harvested but did not receive any component of the study treatment. The non-treated analysis set is not a part of the primary Safety analysis set and will be listed and summarized separately along with the primary reason of not receiving MDA-TIL.

8.3 DESCRIPTION OF STATISTICAL METHODS

8.3.1 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

The primary endpoint for each cohort is the ORR as assessed by investigators using RECIST 1.1 criteria. The ORR is derived as the sum of the number of patients with a confirmed CR or partial response (PR) divided by the number of patients in the All-Treated analysis set x 100%.

8.3.2 ANALYSES OF THE SECONDARY EFFICACY ENDPOINTS

PFS is defined as the time (in months) from the start date of lymphodepletion to PD or death due to any cause, whichever event is earlier. Patients not experiencing PD or death at the time of data cut or end of study (i.e., database lock) will have their event times censored on the last adequate tumor assessment.

DOR is measured from the first time measurement criteria are met for a CR or PR, whichever response is observed first, until the first date that progressive disease (PD) or death occurs. Patients not experiencing PD or death prior to the time of data cut or end of study will have their event times censored on the last adequate tumor assessment. The analysis of DOR is based on responders only as assessed by investigators per RECIST v1.1.

DCR is derived as the sum of the number of patients who achieved PR/CR or SD per the RECIST v1.1 divided by the number of patients in the All-Treated analysis set x 100%.

OS is defined as the time (in months) from the start date of the lymphodepletion to death due to any cause. Patients not having expired at the time of data cut or end of study will have their event times censored on the last date of their known survival status.

The 6- and 12-month landmark survival rates will be calculated based on the Kaplan-Meier method.

8.3.3 ANALYSES OF THE EXPLORATORY ENDPOINTS

All exploratory analyses will be descriptive and performed by cohort. Some analysis results will be reported separated from the final clinical study report.

T-cell repertoire analysis will be used to determine TIL persistence.

Molecular and immunological features of tumors before and after TIL therapy will be determined using exome sequencing and immunohistochemistry/immunofluorescence analyses.

Sensitivity analyses on ORR, DCR, DOR, and PFS as measured by investigators using the irRECIST criteria will be performed.

Pearson correlation coefficient and linear regression, when appropriate, will be used to quantify the relationship between phenotypic attributes (CD8 %, CD27 and CD28 expression, etc.) and tumor response to therapy.

Baseline CA19-9 of patients with PDAC and baseline CA-125 of patients with ovarian cancer will be assessed for potential correlations with the efficacy outcome

8.3.4 SAFETY ANALYSES

Grade 3 or higher treatment-emergent AEs and their incidence rates will be compared descriptively to historical data of TIL in other cancer disease types. AE incidence rates will be estimated with 95% CIs per cohort and all

cohorts combined. The treatment-emergent AEs start from the first dose of cyclophosphamide and up to 6 months from the last dose of IL-2.

We will monitor the probability of not completing TIL administration across all cohorts aggregately using the following Bayesian stopping rule. Let p_{TIL} denote the probability of not completing TIL administration due to toxicities. The stopping rule says that if $Pr(p_{TIL} > 0.3|data) > 0.6$, i.e., if the data suggest that there is more than 60% chance that the rate of not completing TIL administration is greater than 0.3, we suspend the accrual and inspect the safety data with possible termination of the trial. Assuming a vague beta prior that $p_{TIL} \sim Beta(0.3, 0.7)$, the Bayesian stopping rule corresponds to the following stopping boundaries: suspend accrual if

number of patients not completing TIL administration/number of patients treated
>= 2/3, 3/6, 5/12, 8/24, 12/36, 18/54

8.3.5 ADHERENCE AND RETENTION ANALYSES

A study disposition summary will display number and percentages of patients who exit the study early by the primary reason in 2 parts:

1. After the tumor harvest prior to lymphodepletion and
2. On or after the first dose of cyclophosphamide

Patients who are treated and being followed for the survival status at the time of study termination (i.e., completers) are not a part of this summary. Patients who did not receive planned full study treatment doses will also be summarized by its primary reason.

8.3.6 BASELINE DESCRIPTIVE STATISTICS

Baseline demographic and disease characteristics will be summarized descriptively for the Safety and the All-Treated analysis sets. Age will be derived as a function of the date of informed consent.

8.3.7 PLANNED INTERIM ANALYSES

Each cohort will be analyzed for the stage I criteria within first 10 treated patients.

8.3.8 SAFETY REVIEW

The safety parameters will be reviewed on an on-going basis including grades 3 and 4 adverse events (AEs), serious AEs, deaths, treatment-related AEs, AEs that lead to reduced or missed doses of lymphodepletion or IL-2, clinical laboratory tests, vital signs, and physical examinations.

8.3.9 EFFICACY REVIEW

The purpose of ongoing efficacy review is to maintain the accuracy of tumor measures for all target lesions in the clinical database and ensure the consistent follow-up of all target and non-target lesions identified at baseline.

Sub-groups defined by histology and/or potential biomarkers that are unique to each disease cohort will be used to summarize efficacy in addition to all patients per cohort if such analyses are feasible considering the smaller sub-group sample size.

8.3.10 MULTIPLE COMPARISON/MULTIPLICITY

There is no formal statistical comparison and therefore adjustment for multiplicity does not apply to this study.

8.3.11 TABULATION OF INDIVIDUAL RESPONSE DATA

Summary of tumor response data per cohort will be based on the best overall response as assessed by investigators per RECIST 1.1. The summary will display percentages with 80% confidence intervals (CIs) for ORR and 95% CIs for DCR by the Wilson score method among patients in the All-Treated analysis set. The median time-to-event and the landmark rates will also be measured with 95% CIs for DOR, PFS, and OS by the KM method.

8.3.12 EXPLORATORY ANALYSES

All exploratory analyses will be descriptive and performed by cohort. The analysis will be defined separately from the statistical analysis plan for this study and reported independently outside the clinical study report (CSR).

HRQOL will be assessed using the EORTC QLQ-C30 instrument and analyzed per the published evaluation manual.

8.4 SAMPLE SIZE

The Simon's two stage minimax design will be used to monitor the efficacy of each cohort independently. The null hypothesis that the historical response rate of 5% to be tested against the estimated experimental cohort response rate of 20%. In the first stage, 10 patients will be treated per cohort. If there is no confirmed response in these 10 patients, so long as the patient are evaluable, the cohort will be terminated. Other efficacy estimates including maximum % reductions in target lesion sum of diameters and/or time to PD/death may be considered for termination. A confirmed response shall be determined by RECIST 1.1 criteria with first assessment at 6 weeks and second confirmatory scan at 12 weeks. If the study moves forward to Stage II, an additional 8 patients will be treated leading to a total of 18 patients for that cohort. Three or more responders out of 18 treated patients for the cohort will be considered clinically relevant to justify further investigation. The power of this design is >=70% under the 1-sided type I error rate of 10%.

8.5 EFFICACY/TOXICITY SUMMARY REPORTS

The Investigator is responsible for completing efficacy/toxicity summary reports and submitting them to the IND office Medical Affairs and Safety Group for review. These should be submitted as follows:

Stage I: After the first 10 evaluable patients per cohort complete 12 weeks post-initiation of study treatment and

Stage II: After additional 8 evaluable patients per cohort complete 12 weeks post-initiation of study treatment.

9. STUDY DATA MANAGEMENT

9.1 CLINICAL STUDY DATA

Clinical study data for this trial will be collected and managed using Prometheus, a 21CFR11- compliant electronic data capture system. Prometheus is a secure portal that requires users to login with validated credentials, has granular data access controls to ensure that the minimal amount of information required to complete a task is presented, handles the de-linking and de-identification of patient information to maintain

patient confidentiality. Prometheus provides a multi-institute 21 CFR 11 compliant data capture portal to simplify these tasks. Standard data collection, storage procedures, and quality assurance procedures will be followed to ensure integrity and auditability of all information entered.

9.2 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

PBMCs and TIL infusion product will be used for flow cytometry studies. DNA and RNA will also be extracted to be used for TCR sequencing. Leftover tumor tissue from TIL harvest as well as from any biopsies performed after therapy will be used for translational studies and may include flow cytometry studies, DNA and RNA extraction for gene expression studies.

If sufficient biological samples are available and at the discretion of the PI and Iovance Biotherapeutics, samples may be sent to Iovance for additional exploratory studies.

9.3 FUTURE USE OF STORED SPECIMENS

Research material from patients enrolled on this study will be kept at MD Anderson in Dr. Bernatchez's laboratory and Dr. Wistuba's laboratory for the duration of the study. De-identified patient material may be shared with Iovance for testing during the study.

9.4 PUBLICATION AND DATA SHARING POLICY

MD Anderson, through the Principal Investigator, shall provide to Iovance Biotherapeutics interim written reports regarding the Research, no less than once per calendar quarter, and a draft final written study report within thirty (30) days after completion (or earlier termination) of the study. Further subsequent development of the final written study report will follow the terms specified in Study Order or Strategic Alliance Agreement.

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APPENDIX A. EXPECTED ALDESLEUKIN TOXICITIES AND THEIR MANAGEMENT

Expected toxicity	Expected grade	Supportive Measures	Stop Treatment*
Chills	3	IV Meperidine 25-50 mg, IV q1h, prn	No
Fever	3	Acetaminophen 650 mg, po, q4h; Indomethicin 50-75 mg, po, q8h	No
Pruritis	3	Hydroxyzine HCL 10-20 mg po q6h, prn; Diphenhydramine HCL25-50 mg, po, q4h, prn	No
Nausea/ Vomiting/ Anorexia	3	Ondansetron 10 mg, IV, q8h, prn; Granisetron 0.01 mg/kg IV daily prn; Droperidol 1 mg, IV q4-6h, prn; Prochlorperazine 25 mg q4h p.r., prn or 10 mg IV q6h prn	No
Diarrhea	3	Loperamide 2 mg, po, q3h, prn; Diphenoxylate HCl 2.5 mg and atropine sulfate 25 mcg, po, q3h, prn; codeine sulfate 30-60 mg, po, q4h, prn	If uncontrolled after 24 hours despite all supportive measures
Malaise	3 or 4	Bedrest interspersed with activity	If other toxicities occur simultaneously
Hyperbilirubinemia	3 or 4	Observation	If other toxicities occur simultaneously
Anemia	3 or 4	Transfusion with PRBCs	If uncontrolled despite all supportive measures
Thrombocytopenia	3 or 4	Transfusion with platelets	If uncontrolled despite all supportive measures
Neutropenia	4	Observation	No
Edema/Weight gain	3	Diuretics prn	No
Hypotension	3	Fluid resuscitation; Vasopressor support	If uncontrolled despite all supportive measures

Dyspnea	3 or 4	Oxygen or ventilatory support	If requires ventilatory support
Oliguria	3 or 4	Fluid boluses or dopamine at renal doses	If uncontrolled despite all supportive measures
Increased creatinine	3 or 4	Observation	Yes (grade 4)
Renal failure	3 or 4	Dialysis	Yes
Pleural effusion	3	Thoracentesis	If uncontrolled despite all supportive measures
Bowel perforation	3	Surgical intervention	Yes
Confusion	3	Observation	Yes
Somnolence	3 or 4	Intubation for airway protection	Yes
Arrhythmia	3	Correction of fluid and electrolyte imbalances; chemical conversion or electrical conversion therapy	If uncontrolled despite all supportive measures
Elevated Troponin levels	3 or 4	Observation	Yes
Myocardial Infarction	4	Supportive care	Yes
Elevated transaminases	3 or 4	Observation	For grade 4 without liver metastases
Electrolyte imbalances	3 or 4	Electrolyte replacement	If uncontrolled despite all supportive measures

*Unless the toxicity is not reversed within 12 hour