TITLE: PHASE II NEOADJUVANT STUDY OF PD-1 INHIBITOR DOSTARLIMAB (TSR-042) VS. COMBINATION OF TIM-3 INHIBITOR COBOLIMAB (TSR-022) AND PD-1 INHIBITOR DOSTARLIMAB (TSR-042) IN RESECTABLE STAGE III OR OLIGOMETASTATIC STAGE IV MELANOMA (NEO-MEL-T)

SPONSOR: **Diwakar Davar**

PI: **Diwakar Davar**

Study Drug Names: Dostarlimab (TSR-042) and Cobolimab (TSR-022)

Clinical Phase: Phase II

NCT Number: NCT04139902

Protocol date and version: v9 dated 07/09/2026

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Declaration of Sponsor or Responsible Medical Officer

TITLE: Phase II Neoadjuvant Study of PD-1 Inhibitor Dostarlimab (TSR-042) vs. Combination of Tim-3 Inhibitor Cobolimab (TSR-022) and PD-1 Inhibitor Dostarlimab (TSR-042) in Resectable Stage III or Oligometastatic Stage IV Melanoma

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

_____ _____

Dr. Diwakar Davar, MD **Date**

UPMC Hillman Cancer Center

INVESTIGATOR SIGNATURE PAGE / V9 DATED 07/09/2026

Declaration of the Investigator

Title: Phase II Neoadjuvant Study of PD-1 Inhibitor Dostarlimab (TSR-042) vs. Combination of Tim-3 Inhibitor Cobolimab (TSR-022) and PD-1 Inhibitor Dostarlimab (TSR-042) in Resectable Stage III or Oligometastatic Stage IV Melanoma

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Investigator

_____ _____

[Name] **Date**
[Title]
[Institution]

LIST OF ABBREVIATIONS AND DEFINITIONS

Table 1 List of Abbreviations

Abbreviation	Definition
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse even of special interest
AML	acute myeloid leukemia
AUC	area under the curve
BER	base excision repair
BRCA	breast cancer gene
CBC	complete blood count
CL	oral clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DDR	DNA damage repair
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
FE	food effect
gBRCA	germline breast cancer gene
GCSF	Granulocyte-colony stimulating factor
GBM	glioblastoma multiforme
hCG	human chorionic gonadotropin
HR	homologous recombination
HRD	homologous recombination deficiency
irAEIs	immune-related adverse events of interest
IUD	intrauterine device
LLN	Lower limit of normal
MDS	myelodysplastic syndrome
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NHEJ	non-homologous end joining
PARP	poly(ADP-ribose) polymerase
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetics

Abbreviation	Definition
PRO	patient reported outcomes
PS	performance status
QD	once a day
QTc	corrected QT interval
SAE	serious adverse event
TEAS	treatment-emergent adverse events
ULN	upper limit of normal

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1. Trial Summary

Trial Phase	Randomized phase II
Clinical Indication	PD-1 naïve stage III B/C/D and stage IVA melanoma
Trial Type	Neoadjuvant and adjuvant study
Type of control	PD-1 monotherapy (Dostarlimab (TSR-042))
Route of administration	Dostarlimab (TSR-042) (intravenous) Cobolimab (TSR-022) (intravenous)
Trial Blinding	N/A
Treatment Groups	2
Number of trial subjects	Total sample size: 62 patients Sample size per arm: 31 patients
Estimated enrollment period	15-32 months
Estimated duration of trial	24 months
Duration of Participation	24 months
Estimated average length of treatment per patient	Approximately 54 weeks (Pre-Operative Phase 6 weeks; Post-Operative Phase 48 weeks)

2. Trial Design

2.1. Trial Design

This is a randomized phase II neoadjuvant study evaluating neoadjuvant immunotherapy with either PD-1 inhibitor Dostarlimab (TSR-042) or PD-1/TIM-3 inhibitor combination Dostarlimab (TSR-042)/Cobolimab (TSR-022) in patients with resectable regionally advanced or oligometastatic melanoma.

Patients with stage III B/C/D or oligometastatic stage IVA melanoma with lymph node (LN) and/or in-transit and/or oligometastatic disease who have yet to undergo definitive surgery are eligible to enroll. Patients who have received prior adjuvant interferon (IFN) and/or ipilimumab and/or BRAF/MEK inhibitors are eligible to enroll. Patients who have previously received either nivolumab or pembrolizumab or ipilimumab/nivolumab are **NOT** eligible. Other eligibility criteria include but are not limited to measurable disease, presence of disease amenable to biopsy and absence of CNS disease.

Suitable patients will be identified pre-operatively. Patients will undergo screening evaluation consisting of systemic/CNS staging scans, tumor biopsy, blood studies to confirm suitability. Subjects will receive neoadjuvant therapy Dostarlimab (TSR-042) or Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination for 6 weeks prior to planned surgery (**Pre-Operative Phase**). Surgery will occur 1-4 weeks after completion of pre-operative therapy. After recovery from surgery subjects will receive Dostarlimab (TSR-042) (**Post-Operative Phase**) for approximately 48 weeks, for a total of 54 weeks of study drug(s) administration in total.

2.2. Trial Diagram

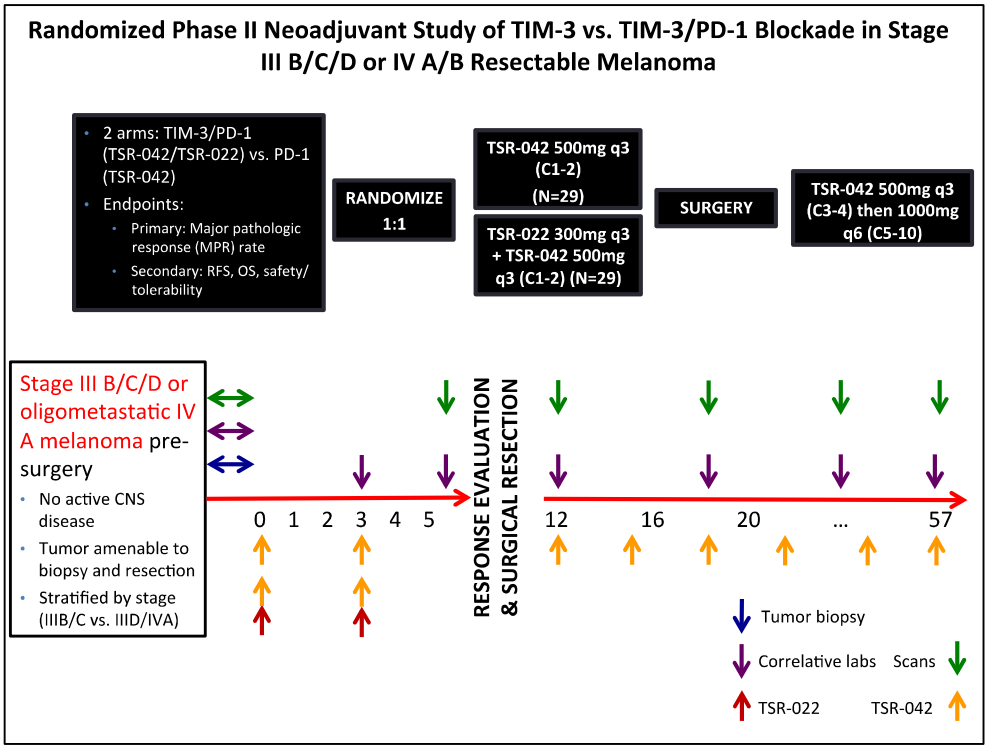


Figure 1: Trial Diagram

3. Objective(s) and Hypothesis(es)

3.1. Primary Objective and Hypothesis

Objective: To evaluate major pathologic response rate (MPR rate) in patients with stage III B/C/D or stage IV A melanoma treated with either neoadjuvant Dostarlimab (TSR-042) or neoadjuvant Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination.

Hypothesis: That the Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination therapy improves MPR rate over historical control in patients with stage III B/C/D or stage IV A melanoma.

3.2. Secondary Objectives

Objective: To evaluate safety, frequency of delay/cancellation in surgery, relapse-free survival (RFS) and overall survival (OS) in patients with stage III B/C/D or stage IV A melanoma following neoadjuvant therapy with either neoadjuvant Dostarlimab (TSR-042) or neoadjuvant Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination.

Hypothesis: That neoadjuvant Dostarlimab (TSR-042) or neoadjuvant Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination is safe, and improves RFS and OS in patients with stage III B/C/D or stage IV A melanoma.

3.3. Exploratory Objectives

Objective: To evaluate circulating and intra-tumoral immune cells, including T-cells (CD8, CD4, Tregs) and antigen-presenting cells (monocytes, macrophages, MDSCs), for the expression of inhibitory and activating receptors and ligands including functional analyses. To evaluate TCR clonality/diversity analyses of circulating and intra-tumoral CD8+ T-cells before and after Dostarlimab (TSR-042) and Cobolimab (TSR-022) administration.

Hypothesis: That neoadjuvant Dostarlimab (TSR-042) or neoadjuvant Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination improves T-cell functionality by augmenting antigen presentation and increasing T-cell infiltrate compared to TSR-022 monotherapy.

4. Background and Rationale

4.1. Background

4.1.1. Pharmaceutical and Therapeutic Background: Dostarlimab (TSR-042)

Intact immune surveillance prevents and controls outgrowth of neoplastic transformation (Disis, 2010). Accumulating evidence shows strong correlation between tumor-infiltrating lymphocytes (TIL) in cancer tissue and improved prognosis in various malignancies (Mei et al., 2014; Schatton et al., 2014; Gooden et al., 2011; Schreiber et al., 2011; Bremnes et al., 2011; Talmadge, 2011; Shirabe et al., 2010; Nosho et al., 2010; Bellati et al., 2009; Oble et al., 2009; Uppaluri et al., 2008; Dunn et al., 2007). In particular, the presence of cluster of differentiation (CD)8+ T cells and the ratio of CD8+ effector T cells:FoxP3+ regulatory T cells seem to correlate with improved prognosis and long-term survival in many solid tumors (Nosho et al., 2010; Chang et al., 2014; Preston et al., 2013; Yoon et al., 2012; Kim et al., 2013; Mathai et al., 2012; Liu et al., 2011; Kirk, 2010).

The programmed death-1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control (Pedoeem et al., 2014). The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (programmed death-ligand 1 [PD-L1] and programmed death-ligand 2 [PD-L2]). The structures of murine PD-1 alone (Zhang et al., 2004) and in complex with its ligands were the first to be resolved (Lázár-Molnár et al., 2008; Lin et al., 2008) and more recently the nuclear magnetic resonance-based structure of the human PD-1 extracellular region and analyses of its interactions with its ligands were also reported (Cheng et al., 2013). PD-1 and family members are Type I transmembrane glycoproteins containing an Ig variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail, which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM), and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T cell signaling cascade (Sheppard et al., 2004). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4 (Ott, PA et al. 2013). PD-1 was shown to be expressed on activated lymphocytes,

including peripheral CD4+ and CD8+ T cells, B cells, T regs, and natural killer cells (Yao and Chen, 2014). Expression has also been shown during thymic development on CD4-/CD8- (double-negative) T cells (Nishimura et al., 1996), as well as subsets of macrophages (Huang et al., 2009) and dendritic cells (Peña-Cruz et al., 2010). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types (Keir et al., 2008). PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is predominantly expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments (Keir et al., 2008). Both ligands are Type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T cell receptor. PD-L2 is thought to control immune T cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor (Guan et al., 2017; Taube et al., 2012), which, via its interaction with the PD-1 receptor on tumor-specific T cells, plays a critical role in immune evasion by tumors (Sanmamed and Chen et al., 2014). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer (Topalian et al., 2012).

Single-agent PD-1/PD-L1 blockade is efficacious in a variety of advanced cancers including melanoma (Weber et al., 2015; Robert et al., 2015; Wolchok et al., 2017; Robert et al., 2015a; Ribas et al., 2015) , non small cell lung cancer (Brahmer et al., 2015; Borghaei et al., 2015; Gandhi et al., 2018; Reck et al., 2016; Herbst et al., 2016), Hodgkin lymphoma (Armand et al., 2018; Lesokhin et al., 2016; Chen et al., 2017; Zinzani et al., 2017), renal cell carcinoma (Motzer et al., 2015), head/neck cancer (Ferris et al., 2016; Seiwert et al., 2016), urothelial carcinoma (Sharma et al., 2017; Balar et al., 2017), microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (Overman et al., 2017), MSI-H/dMMR tumors regardless of histology (Seiwert et al., 2016; Alley et al., 2017; Le et al., 2018; Chung et al., 2018; Diaz et al., 2016), hepatocellular carcinoma (El-Khoueiry et al., 2017), cervical cancer (Chung et al., 2018a) and gastric cancer (Fuchs et al., 2016). In the adjuvant setting in melanoma, PD-1 inhibitors nivolumab (Weber et al., 2017) and pembrolizumab (Eggermont et al., 2018) improve RFS and OS in melanoma.

Dostarlimab (TSR-042) is an IgG4 humanized monoclonal antibody that binds with high affinity to PD-1, resulting in inhibition of binding to PD-L1 and PD-L2. This antibody was generated based on a proprietary platform that utilizes affinity maturation to select highly-specific antibodies with desired functional characteristics. The functional antagonist activity of Dostarlimab (TSR-042) was confirmed in a mixed lymphocyte reaction assay, demonstrating enhanced interleukin-2 (IL-2) production upon addition of Dostarlimab (TSR-042). Furthermore, Dostarlimab (TSR-042) has an acceptable safety profile based on toxicology studies in cynomolgus monkeys. Additional information on the nonclinical and clinical experience with Dostarlimab (TSR-042) can be found in the Dostarlimab (TSR-042) IB.

4.1.2. Non clinical data Dostarlimab (TSR-042)

Dostarlimab (TSR-042) binds with high affinity to human and cynomolgus monkey PD-1. Dostarlimab (TSR-042) blocks binding of soluble ligands to human PD-1 expressed on the surface of Chinese hamster ovary cells, with a 50% maximum inhibitory concentration (IC_{50}) of approximately 1 nM. TSR-042 enhances T cell activation, as measured by the production of IL-2from activated CD4+ T cells, with a 50% maximum effective concentration (EC_{50}) of approximately 1 nM. Full PD-1 receptor occupancy achieved by Dostarlimab (TSR-042) in human and cynomolgus monkey T cells

from peripheral blood mononuclear cells was determined to occur at concentrations of approximately 1 μg/mL.

Linear pharmacokinetic (PK) was observed for Dostarlimab (TSR-042) over the dose range tested of 10 to 100 mg/kg. Sex had no effect on exposure. The volume of distribution at steady state was low and suggested minimal tissue penetration, which is commonly observed for therapeutic monoclonal antibodies. Weekly administration resulted in approximately 2- to 3-fold increase in TSR-042 exposure.

Administration of Dostarlimab (TSR-042) by a weekly IV dose (5 total doses) to cynomolgus monkeys at doses of 0, 10, 30, or 100 mg/kg was well tolerated and did not result in any TEAEs on clinical signs, body weight, food consumption, ECG, ophthalmology, safety pharmacology parameters, clinical pathology, gross pathology, organ weight, or histopathology. The no-observed-adverse-effects level was ≥100 mg/kg in this study.

4.1.3. Clinical data Dostarlimab (TSR-042)

Dostarlimab (TSR-042) has been evaluated in the ongoing phase I study 4010-01-001 (GARNET) that is evaluating the safety and tolerability, PK, pharmacodynamics, and clinical activity of TSR-042 evaluate in patients with advanced solid tumors (Moreno et al., 2018). The study was conducted in 2 parts:

- Part 1 (dose escalation) of the study used a modified 3 + 3 design to evaluate 3 ascending weight-based doses of Dostarlimab (TSR-042) as follows: 1, 3, and 10 mg/kg administered every 2 weeks (Q2W) via IV infusion.
- Part 2 of the study is being conducted in 2 subparts (Part 2A and Part 2B) to explore the safety and clinical activity of TSR-042 administered as a fixed dose (ie, not weight based).
  - In Part 2A, following the completion of Part 1, the safety and tolerability of Dostarlimab (TSR-042) were evaluated at fixed doses of 500 mg every 3 weeks (Q3W) and 1,000 mg every 6 weeks (Q6W) using a modified 6 + 6 design with up to 24 patients (6 patients/cohort).
  - In Part 2B, the clinical activity, tolerability, and safety of Dostarlimab (TSR-042) at the RP2D will be evaluated in patients with specific tumor types. Up to 5 tumor types may be investigated in 6 expansion cohorts with approximately 65 patients enrolled in each cohort.

As of 21 January 2019, a total of 627 patients have received at least 1 dose of dostarlimab in the 4010-01-001 (GARNET) study. There were 18 on-study deaths and 52 study drug discontinuations due to AEs.

Of the 335 subjects treated with dostarlimab monotherapy in 4010-01-001 (GARNET) study, 93.7% reported at least 1 TEAE, with events of fatigue, nausea, and diarrhoea being the most frequently reported. Study drug related TEAEs of Grade ≥3 were reported in 36 subjects (10.7%). SAEs occurred in 106 subjects (31.6%); in 21 of these subjects, these SAEs were considered study drug-related. Of the 292 subjects treated with dostarlimab in combination with other therapeutic agents, 94.5% reported at least 1 TEAE, with events of fatigue, nausea, and dyspnoea being the most frequently reported. SAEs occurred in 108 subjects (37.0%), and for 20 of 108 subjects, the SAEs were related to the study drug.

As of March 13, 2019, 125 patients with endometrial cancer were enrolled to and treated with dostarlimab monotherapy in Part 1 and Part 2A of 4010-01-001 (GARNET). Of these 125 patients who were response-evaluable, 41 were MSI-H (33%), while 79 were MSS (63%) patients,while 5 had unknown MSI-status (4%). Overall response rates by irRECIST in the full population, MSI-H population, and MSS population were 30%, 49%, and 20%, respectively. Disease control rate in the full population, MSI-H population, and MSS population was 53%, 63% and 47%, respectively.

Given this encouraging clinical activity in heavily pretreated patients with diverse tumor types, and the manageable safety profile of dostarlimab, the benefit-risk profile for use of dostarlimab for treatment of patients with advanced cancers appears positive. Clinical activity of dostarlimab monotherapy in specific tumor types is being further investigated in Part 2B of 4010-01-001 (GARNET) study. Clinical activity of dostarlimab in combination with other therapies in specific tumor types is being further investigated.

4.1.4. Pharmaceutical and Therapeutic Background for Cobolimab (TSR-022)

T cell immunoglobulin and mucin domain 3 (TIM-3) is a member of the TIM gene family and is expressed on IFN gamma producing CD4+Th1 and CD8+ Tc1 cells in addition to regulatory and innate T cells (Du et al., 2017; Anderson, 2014). Early studies in autoimmune models clarified that TIM-3 blockade enhanced severity of autoimmune encephalitis, a Th1 dependent process (Monney et al., 2002). Subsequent work clarified the role of TIM-3 and its ligandsin mediating tolerance to chronic antigen stimulation (Sánchez-Fueyo et al., 2003). Since that time TIM-3 has been studied as a negative regulator of T cell function in tumor evasion.

TIM-3 is expressed in a variety of cancers including melanoma, hepatocellular, cervical, colorectal, non-small cell lung (NSCLC), head/neck, renal cell, esophageal, prostate and non-Hodgkin's lymphoma (Du et al., 2017). While TIM-3 has multiple ligands including galectin-9, Ceacam-1, HMGB-1 and phosphatidyl serine (Anderson et al., 2016), most studies have investigated its interaction with galectin-9. As a co-inhibitory molecule, TIM-3's interaction with its ligand (s) has been shown to suppress T cell response and thus aid in the evasion of tumor by the immune system (Das et al., 2017). Interaction of TIM-3 with ligand galectin-9 has even been shown to result in Th1 cell death further corroborating a role as a negative regulator of anti-tumor immunity (Zhu et al., 2005).

TIM-3 has been postulated to play a role in T cell exhaustionin murine and human models. In a study conducted in TIM-3 transgenic mice, overexpression of TIM-3 along with ligand galectin-9 resulted in a curbed immune response while loss of TIM-3 restored immune function (Dardalhon et al., 2010). In human melanoma, TIM-3 was associated with exhausted CD8+ T cells, and TIM-3 blockade restored CD8+ T cell function (Fourcade et al., 2010).

The possibility of enhancing clinical activity of tumor immunotherapy through TIM-3 blockade supports the value of targeting TIM-3 in combination with PD-1 blockade.

Cobolimab (TSR-022) is an IgG4-k isotype humanized monoclonal antibody that binds with high affinity to TIM-3 resulting in enhanced T cell activity in ex vivo T cell stimulation assays. This antibody was generated based on a proprietary platform that utilizes affinity maturation to select antibodies with desired functional characteristics.

4.1.5. Nonclinical Data for Cobolimab (TSR-022)

The functional antagonist activity of Cobolimab (TSR-022) was confirmed in both a mixed lymphocyte reaction (MLR) and an anti-CD3/28 T cell stimulation assay demonstrating enhanced IL-2 production upon addition of Cobolimab (TSR-022). The addition of an anti-PD1 antibody further enhanced IL-2 secretion reflecting increased T cell activation with concurrent blockade of TIM-3 and PD-1 compared to blockade of either protein alone. In addition to enhancing T cell activity, Cobolimab (TSR-022) has an acceptable safety profile based on toxicology studies in cynomolgus monkeys.

4.1.6. Clinical Data for Cobolimab (TSR-022)

Based on the pre-clinical data identifying TIM-3 expression on tumor infiltrating T cells in a broad range of tumors and TIM-3 blockade resulting in enhanced T cell activity, Cobolimab (TSR-022) is expected to result in clinical activity in patients with a variety of tumors and thus Cobolimab (TSR-022) is being advanced for clinical development as an immunotherapy for advanced malignancies. To date, 18 patients have been treated at dose levels of 0.03, 0.1, 0.3 and 1 mg/kg, and there have been no DLTs observed.

In this study, patients will receive Cobolimab (TSR-022) at 300mg Q3W based on pharmacokinetic modeling and clinical data from patients treated in the 4020-01-001 (AMBER) study.

4.2. Rationale

4.2.1. Rationale for Combination of PD-1 Inhibitor and Tim-3 Inhibitor

PD1 blockade has been shown to be effective in reversing T cell dysfunction and restoring tumor-specific T cell responses in a variety of cancers (Yamamoto et al., 2008; Zhang et al., 2009). Monoclonal antibodies targeting PD-1/PD-L1 immune checkpoints have produced durable responses in a variety of cancers including melanoma (Ribas et al., 2016; Larkin et al., 2015). However, more than half of all melanoma patients do not respond to PD-1 or PD-1/CTLA-4 combination. PD-1 non-response may be due to several factors including intestinal dysbiosis (Gopalakrishnan et al., 2018; Matson et al., 2018; Routy et al., 2018) upregulation of alternative inhibitory receptors such as Tim-3, TIGIT and LAG-3 (Fourcade et al., 2010; Chauvin et al., 2015) (Woo et al., 2012), increased oncogenic signaling through pathways such as WNT-β-catenin (Spranger et al., 2015) and loss of type I IFN signaling (Zaretsky et al., 2016) amongst others (Pitt et al., 2016).

Several lines of evidence suggest the Tim-3 blockade may improve upon the benefit of PD-1 blockade. Firstly, cells co-expressing Tim-3 and PD-1 were the dominant (compared to PD1 or TIM-3 alone) and most functionally exhausted (based on IL-2, TNF and INF-γ production upon cytokine stimulation) fraction of tumor infiltrating lymphocytes (TILs) in cancer bearing mice (Sakuishi et al., 2010). Secondly, combined blockade of Tim-3 and PD-1 in these mice had greater effects upon tumor growth and INF-γ production than either PD-1 or Tim-3 blockade singly. Finally, in *ex vivo* studies utilizing NY-ESO-1 positive melanoma tumors, combined Tim-3 and PD-1 blockade enhanced cytokine production and proliferation of antigen-specific CD8+ T cells upon prolonged antigen stimulation (Fourcade et al., 2010; Fourcade et al., 2014).

These data suggest that the combination of anti-Tim-3 and anti-PD-1 may address *de novo* resistance to anti-PD-1 blockade while preventing one of the mechanisms that may result in resistance to anti-PD-1 monotherapy.

4.2.2. Clinical data for Cobolimab (TSR-022) and Dostarlimab (TSR-042) combination

Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination has been evaluated in advanced cancer patients in the ongoing AMBER (4002-01-001) study. In part 1c dose escalation of Cobolimab (TSR-022) in combination with TSR-042, 22 patients with various types of cancers were enrolled in the dose level of Cobolimab (TSR-022) (900 mg) in combination with TSR-042 (500 mg). There were no DLTs reported at this recommended Phase 2 dose (RP2D). There was no dose-dependence demonstrated on the incidence of AE or grade 3 or higher AEs regardless of causality to the study medication across the 3 different dose levels of Cobolimab (TSR-022) (100mg, 300mg and 900mg).

In Part 2 (anti-PD(L)1 experienced NSCLC and melanoma patients and CRC patients) 149 patients were treated with 3 dose levels of Cobolimab (TSR-022) in combination with TSR-042 (500mg), 28 patients with 100mg Cobolimab (TSR-022), 92 patients with 300mg Cobolimab (TSR-022) and 29 patients with 900mg Cobolimab (TSR-022) (Davar et al., 2018). There was no dose-dependence demonstrated on the incidence of AE or grade 3 or higher AEs regardless of causality to the study medication across different dose levels of Cobolimab (TSR-022). The most commonly reported AEs regardless of causality are: fatigue, dyspnea, decreased appetite and nausea.

In conclusion, there is no increased incidence of AE at the Cobolimab (TSR-022) R2PD of 900mg relative to lower doses of Cobolimab (TSR-022) (100mg and 300mg) in combination of TSR-042 (500mg). ORRs of 12-18% were reported in the PD-1 R/R setting in melanoma and NSCLC (Davar et al., 2018). Based on pharmacokinetic modeling and clinical data from patients treated in the 4020-01-001 (AMBER) study, the recommended phase II dose (RP2D) of Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination is TSR-042 500mg and TSR-022 300mg Q3W.

4.2.3. Rationale for Study Population

Patients with regionally advanced (stage III B/C/D) or oligometastatic (stage IV A) melanoma based on the AJCC 8th edition staging classification are eligible to enroll. Patients with stage IIIB or greater disease have a high risk of and/or mortality following curative surgery. PD-1 inhibitors nivolumab and pembrolizumab have improved RFS in large phase III adjuvant studies of high-risk resected melanoma. In KEYNOTE-054/EORTC 1345, adjuvant pembrolizumab administered for 1 year improved RFS (HR 0.57; 12-month RFS rate 75.4% versus 61.0% and; 18-month RFS rate 71.4% vs. 53.2%) compared to matched placebo in 1019 stage IIIA-IIIC melanoma patients (Eggermont et al., 2018). Similarly, adjuvant nivolumab improved RFS in resected stage IIIB/C/D or stage IV melanoma compared to ipilimumab in CheckMate-238 (Weber et al., 2017). Specifically in the resected stage IV patient population studied in CheckMate-238, superiority of nivolumab relative to ipilimumab was maintained.

Pre-clinically, compelling data suggests that neoadjuvant immunotherapy has greater therapeutic efficacy compared with adjuvant immunotherapy in eradcating distant metastases following primary tumor resection (Liu et al., 2016). In studies of melanoma patients treated with neoadjuvant immunotherapy (Huang et al., 2018, Amaria et al., 2018, Rozeman et al., 2017, Blank et al., 2018), response to neoadjuvant immunotherapy correlated with RFS at 1-year.

This trial is to be conducted in patients with regionally advanced or oligometastatic disease (resectable stage III/IV) melanoma patients with nodal, and distant skin/LN/in-transit metastases. The standard treatment for regionally advanced melanoma is surgical resection followed by adjuvant

immunotherapy. Population based studies suggest that patients with oligometastatic melanoma with distant skin/LN/subcutaneous (M1A) involvement have similar survival as patients with highest risk regional metastatic (stage III C/D) disease (Hanna et al., 2018; Russo et al., 2018). As such, , it is reasonable to offer a surgical resection followed by adjuvant immunotherapy to these patients. The study will not enroll patients with distant lung and/or visceral metastases.

4.2.4. Rationale for Using Major Pathologic Response (MPR) Rate as a Primary Endpoint with RFS as a Secondary Endpoint

In breast cancer, pathologic complete response (pCR) has been used in neoadjuvant clinical trials as a primary endpoint for accelerated approval of drugs. NEOSPHERE was a multicenter, open-label, randomized phase II trial in which 417 women with HER2-positive early breast cancer were randomized to receive a variety of chemotherapy regimens with and without pertuzumab before and after surgery powered on a primary pCR endpoint (Gianni et al., Lancet Oncol 2012). The combination of pertuzumab, trastuzumab and docetaxel (group B) had significantly improved pCR (45.8%) compared to the others (group A: trastuzumab/docetaxel; group C: pertuzumab/trastuzumab; group D: pertuzumab/docetaxel) and led the accelerated approval of pertuzumab. Subsequent full approval was granted following a meta-analysis that reported significant association of pCR with improved survival outcomes in pooled analyses of multiple neoadjuvant trials in breast cancer (Cortazar et al., 2014).

In the context of melanoma, several agents in the melanoma armamentarium have been evaluated in the neoadjuvant context including: high dose interferon (Moschos et al., 2006), ipilimumab (Tarhini et al., 2016; Tarhini et al., 2014), pembrolizumab (Huang et al., 2018), nivolumab (Amaria et al., 2018) and nivolumab/ipilimumab (Rozeman et al., 2017; Blank et al., 2018). In the context of nivolumab and nivolumab/ipilimumab, pCR rates reported range from 25% (nivolumab) to 45% (nivolumab/ipilimumab). While earlier neoadjuvant studies in melanoma reported pCR utilizing criteria to define the residual volume of tumor (RVT) derived from neoadjuvant studies of chemotherapy (Hellmann et al., 2014), more recent studies have utilized new criteria as delineated below.

Neoadjuvant use of immuno-oncologic agents results in distinct histopathologic features compared to neoadjuvant chemotherapy. Specifically, neoadjuvant PD-1 therapy produces unusual features beyond CD8+ T cell infiltrate and tumor necrosis previously associated with response (Tumeh et al., 2014) including features in areas adjacent to the actual tumor – a location termed “the regression bed”. Histopathologic features associated with response herein include neovascularization; proliferative fibrosis; presence of cholesterol clefts; development of tertiary lymphoid structures; presence of plasma cells, giant cells, foamy macrophages and granulomas (Cottrell et al., 2018). This observations have led investigators to propose new criteria – immune related pathologic response criteria (irPRC) – wherein immune related RVT (% irRVT) is defined as the total surface area of RVT divided by the total tumor bed area (comprising regression bed area + RVT area + areas of necrosis) (Tetzlaff et al., 2018; Cottrell et al., 2018). Compared to standard RVT, irRVT had lower inter-observer variability better correlated with imaging assessments.

Primary endpoint of this study is MPR rate, where MPR is defined as ≤10% RVT remaining in post-therapy specimen using immunotherapy-specific criteria (irRVT) (Tetzlaff et al., 2018; Cottrell et al., 2018).

After a complete resection of melanoma lesions, there is no measurable disease to follow. Surveillance scans are undertaken to monitor for disease recurrence, either regionally or distantly. Although the primary endpoint of this study is MPR rate as defined above, a key secondary endpoint is RFS as one goal of the study is to ascertain whether prophylactic immunotherapy after a complete resection prevents recurrence.

4.2.5. Rationale for Duration of Therapy

There is no consensus regarding the optimal treatment duration for melanoma patients treated in the adjuvant setting. For trials of interferon, various treatment frequencies and durations have been investigated (ranging between 6 months and 5 years) (McArthur et al., 2013). There remains significant geographic variability in the duration of interferon therapy, usually ranging between 1 and 1.5.

In the EORTC 18071 adjuvant study, although the protocol specified treatment duration was 3 years, the median number of doses received in ipilimumab arm was 7, corresponding to approximately 1 year duration of treatment (Eggermont et al., 2015). 48.8% of subjects in the ipilimumab arm discontinued treatment due to adverse events related to study drug. In both the CheckMate-238 and KEYNOTE-054/EORTC 1345 studies (Weber et al., 2017) (Eggermont et al., 2018), the duration of nivolumab and pembrolizumab respectively was 1 year.

Based on the above, in order to minimize toxicity leading to discontinuation of study drug while maintaining expected efficacy of either study drug, the decision was reached to limit the duration of study therapy in either arm to 1 year.

5. Participant Selection

5.1. Entry Criteria

5.1.1. Diagnosis/Conditions for Study Entry

Patients eligible for this study should have regionally advanced and/or oligometastatic melanoma that is considered ***resectable*** with biopsy-amenable tumor at baseline. All patients should be reviewed initially by an appropriate surgical oncologist to have this documented during enrollment.

5.1.2. Subject Inclusion Criteria

A patient must meet all of the following criteria to be eligible to participate in this study:

1. Be willing and able to provide written informed consent for the study.

2. Be ≥ 18 years of age on day of signing informed consent.

3. Diagnosis of histologically or cytologically confirmed diagnosis of cutaneous or unknown primary melanoma (excluding uveal/choroidal and mucosal melanoma; although acral melanoma is included) belonging to one of the following AJCC 8th edition TNM stages:
   a. T_x or T_{1-4} **AND**
   b. N_{1b}, or N_{1c}, or N_{2b}, or N_{2c}, or N_{3b}, or N_{3c} **AND/OR**
   c. M_{1a}, or M_{1b}

   Patients are eligible for this trial either at presentation for primary melanoma with

concurrent regional nodal and/or in-transit metastasis and/or oligometastasis; **AND/OR** at the time of clinical detected nodal and/or in-transit and/or oligometastatic recurrence; **and may belong to any of the following groups:**

a. Primary melanoma with clinically apparent regional lymph node metastases (deemed ***resectable***).
b. Clinically detected recurrent melanoma at the proximal regional lymph node(s) basin (deemed ***resectable***).
c. Clinically detected primary melanoma involving multiple regional nodal groups (deemed ***resectable***).
d. Clinical detected nodal melanoma (if single site) arising from an unknown primary (deemed ***resectable***).
e. In-transit and/or satellite metastases with or without regional lymph node involved permitted if deemed ***resectable*** at baseline.
f. Distant skin and/or in-transit and/or satellite metastases with or without regional lymph node involved permitted if deemed ***resectable*** at baseline.
    a) The site/number of resectable lesions should be recorded on the initial case report form.
g. Oligometastatic lung disease with or without regional lymph node involved permitted if deemed ***resectable*** at baseline.
    a) The site/number of resectable lesions should be recorded on the initial case report form.
h. NOTE: Determination of ***resectability*** must be made at baseline to be eligible for this neoadjuvant study.

4. Presence of measurable disease based on RECIST 1.1.
5. Have provided tumor tissue from a newly obtained core, punch, incisional or excisional tumor biopsy. Patients must undergo biopsy (core, punch) or open biopsy (incisional, excisional) within 4 weeks of registration on the study.
6. Performance status of 0 or 1 on the ECOG Performance Scale.
7. Demonstrate adequate organ function as defined in **Table 5.1.2-1** performed on screening labs obtained within 14 days of registration.

Table 5.1.2-1: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Platelets	≥100,000 / mcL
Renal	
Serum creatinine **OR** Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels >1.5 x institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or	≤1.5 X ULN unless subject is receiving anticoagulant

Prothrombin Time (PT)	therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

8. Female subject of childbearing potential should have a negative serum pregnancy test within 1 week prior to receiving the first dose of study medication and use an adequate method of contraception starting with the first dose of study therapy through 26 weeks after the last dose of study therapy. See **Section 6.4.3** for a list of acceptable birth control methods.
   Non-childbearing potential is defined as follows (by other than medical reasons):
   - ≥45 years of age and has not had menses for >1 year
   - Patients who have been amenorrhoeic for <2 years without history of a hysterectomy and oophorectomy must have a follicle stimulating hormone value in the postmenopausal range upon screening evaluation
   - Post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must be willing to use an adequate method of contraception throughout the study and for 26 weeks after the last dose of study therapy.
     Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.

9. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 26 weeks after the last dose of study therapy. See **Section 6.4.3** for a list of acceptable birth control methods.

5.1.3. Subject Exclusion Criteria

The subject will not be eligible for study participation if any of the following criteria are met:

1. Patients with uveal and/or mucosal melanoma histology are excluded.

   a. Patients with melanoma of unknown histology are permitted to enroll after discussion with Principal Investigator.

2. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

3. Is receiving systemic immunosuppression with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications for active autoimmune disease.

   a. Note: Patients with a history of active autoimmune disease requiring systemic treatment within the past 3 months *or* a documented history of clinically severe autoimmune disease, *or* a syndrome that requires systemic steroids (>10mg daily prednisone or equivalent) *or* systemic immunosuppressive agents are excluded.

b. Note: Subjects with vitiligo *or* resolved childhood asthma/atopy *or* those with inactive/minimally active disease who have received clearance from a consultant rheumatologist to participate are exceptions to this rule.

c. Note: Subjects that require intermittent use of bronchodilators or local steroid injections are not to be excluded from the study.

4. Has experienced ≥CTCAE grade 3 immune-related AE (irAE) with prior immunotherapy, with the following exceptions.

   a. Subjects who developed non-clinically significant lab abnormalities (elevations in lipase, amylase not associated with clinically significant disease etc.) even if ≥CTCAE grade 3 may enroll if resolved at this time.

   b. Subjects who developed autoimmune disorders of Grade ≤3 may enroll if the disorder has resolved to Grade ≤1.

   c. Note: Subjects who require steroids for autoimmune (or other) disorders are permitted to enroll if steroids requirements are ≤prednisone 10mg daily (or equivalent).

   d. Note: Subjects whose irAEs have resolved *or* are well controlled (i.e.: hypothyroidism stable on hormone replacement etc) are permitted to enroll.

5. Has received prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   a. Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

   b. Note: If subject received surgery, they must have recovered adequately from complications prior to starting therapy.

   c. Note: Subjects with autoimmune disorders of Grade 4 while on prior immunotherapy will be excluded.

6. Has active (i.e., symptomatic or growing) central nervous system (CNS) and/or leptomeningeal metastases.

   a. Note: Patients with CNS lesions that are treated and deemed stable (repeat imaging study done at least 2 weeks prior to first dose of study treatment) are **NOT** permitted to enroll even if other inclusion criteria are met and patients are neurologically asymptomatic.

7. Has a known additional malignancy that is progressing or requires active treatment.

   a. Note: 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.

   b. Note: Patients with invasive cancer diagnosed and treated greater than 2 years prior to current presentation can be enrolled.

   c. Note: Patients with other indolent malignancies that are not progressing and/or deemed to require active therapy may enroll if other inclusion criteria are met.

8. Has evidence of interstitial lung disease or active, non-infectious pneumonitis.

9. Has an active infection requiring systemic therapy.

10. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, chronic obstructive pulmonary disease, uncontrolled major seizure disorder, unstable spinal cord compression, or superior vena cava syndrome).

11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 26 weeks after the last dose of trial treatment.

13. Has a live vaccine within 30 days of initiating protocol therapy.

14. Has received prior therapy with an IDO inhibitor, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 and/or combination (including nivolumab, pembrolizumab or ipilimumab/nivolumab).

   a. Note: Prior treatment with ipilimumab or interferon alfa is allowed.
   b. Note: Patients with history of allergic or hypersensitivity reaction to components or excipients of Dostarlimab (TSR-042) and Cobolimab (TSR-022), interferon alfa or ipilimumab are also excluded.

15. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

16. Has known history of or screening test that is positive for hepatitis B virus (HBV; eg, HBsAg reactive or HBV DNA detected) or hepatitis C virus (HCV; HCV antibody positive and/or HCV RNA quantitative is detected).

   a. Note: Hepatitis C antibody–positive subjects who received and completed treatment for hepatitis C that was intended to eradicate the virus may participate if hepatitis C RNA levels are undetectable.
   b. Note: Hepatitis B positive subjects who received and completed treatment for hepatitis B that was intended to eradicate the virus may participate if hepatitis B DNA levels are undetectable.

6. Treatment Plan

6.1. Treatment

6.1.1. Method of Treatment Assignment

Patients will be randomized in a 1:1 manner to either neoadjuvant Dostarlimab (TSR-042) or to monotherapy combination of Dostarlimab (TSR-042) plus Cobolimab (TSR-022) in the Pre-Operative Phase. In the Post-Operative Phase, all patients will receive Dostarlimab (TSR-042).

6.1.2. Treatment Regimen

Dostarlimab (TSR-042) only arm:

- Pre-Operative Phase: Dostarlimab (TSR-042) 500mg Q3W for 2 cycles (cycles 1-2). During this period, missed doses will not be made up.
- Post-Operative Phase: Dostarlimab (TSR-042) 500mg Q3W for 4 doses (cycles 3-4) and 1000mg Q6W for 6 doses (cycles 5-10). During this period, missed doses will be made up.

Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination arm:

- Pre-Operative Phase: Cobolimab (TSR-022) 300mg Q3W and Dostarlimab (TSR-042) 500mg Q3W for 2 cycles (cycles 1-2). During this period, missed doses will not be made up.
- Post-Operative Phase: Dostarlimab (TSR-042) 500mg Q3W for 4 doses (cycles 3-4) and 1000mg Q6W for 6 doses (cycles 5-10). During this period, missed doses will be made up.

6.1.3. Dostarlimab (TSR-042) Dose selection/administration

For patients receiving Cobolimab (TSR-022)/Dostarlimab (TSR-042) combination, Cobolimab (TSR-022) will be administered first followed by Dostarlimab (TSR-042). For patients receiving only Dostarlimab (TSR-042), Dostarlimab (TSR-042) will be administered as a single agent.

Dostarlimab (TSR-042) will be administered via a 30-minute (5-minute/+15-minute infusion window allowed) IV infusion at 500mg on Day 1 of every cycle. In the Pre-Operative Phase, a cycle is 3 weeks long, while in the Post-Operative Phase, a cycle is 6 weeks in length.

There will be no dose escalations or reductions of Dostarlimab (TSR-042) allowed. Pre-medications are not recommended. Participants should be carefully monitored for infusion reactions during administration. Dostarlimab (TSR-042) will be administered after all procedures/assessments have been completed as detailed on the trial flow chart. All trial treatments will be administered on an outpatient basis.

6.1.4. Cobolimab (TSR -022) Dose selection/administration

For patients receiving Cobolimab (TSR-022)/Dostarlimab (TSR-042) combination, Cobolimab (TSR-022) will be administered first followed by TSR-042. For patients receiving only Dostarlimab (TSR-042), Cobolimab (TSR-022) will not be administered. In the former, Cobolimab (TSR-022) will be administered first via a 30-minute (5-minute/+15-minute infusion window allowed) IV infusion on Day 1 of every 21-day cycle (ie, Q3W) at 300 mg followed by TSR-042.

There will be no dose escalations or reductions of Cobolimab (TSR-022) allowed. Premedications are not recommended. Participants should be carefully monitored for infusion reactions during

administration. Cobolimab (TSR-022) will be administered after all procedures/assessments have been completed as detailed on the trial flow chart. All trial treatments will be administered on an outpatient basis.

6.2. Treatment Allocation

Up to 62 patients, will be randomized in a 1:1 fashion to receive either of the following in the Pre-Operative Phase:

- Dostarlimab (TSR-042) monotherapy
- Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination therapy

The randomization will be conducted using the UPCI biostatistics randomizer, an intranet application for randomizing patients on different treatment arms for various UPCI clinical trials.

6.3. Stratification

Patients will be stratified by stage (IIIB/C vs. IIID/IV-A).

6.4. Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the principal investigator. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the treating physician investigator, the principal investigator, and the subject.

6.4.1. Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.
All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in **Section 10.5**.

6.4.2. Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol

- Chemotherapy not specified in this protocol
- Investigational agents
- Any surgery that involves tumor lesions

Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The exclusion criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the **Post-Treatment Follow-up Phase**.

Medications intended solely for supportive care (i.e., antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

6.4.3. Birth control

Participants of childbearing potential who are sexually active and their partners must agree to the use of a highly effective form of contraception throughout their participation beginning with time of consent, during the study treatment and for 26 weeks after last dose of study treatment(s):

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral route
  - Intravaginal route
  - Transdermal route
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion

- Vasectomized partner
- Sexual abstinence, if the preferred and usual lifestyle of the subject

6.5. Breast Feeding / Blood Donation

Participants must not breast-feed while receiving protocol therapy and for 26 weeks following the last dose of protocol therapy. Participants must not donate blood during the study or for 90 days after the last dose of protocol therapy.

6.6. Rescue Medications and Supportive Care

6.6.1. Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to either Cobolimab (TSR-022) or Dostarlimab (TSR-042).

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below).

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Pneumonitis**
  - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis**
  - Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
    - For **T1DM** or **Grade 3-4** Hyperglycemia
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis**
    - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
    - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hyperthyroidism or Hypothyroidism**
    - Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
    - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
        - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
    - **Grade 3-4** hyperthyroidism
        - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hepatic**
    - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
        - Treat with IV or oral corticosteroids
    - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
        - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Nephritis**
    - For **Grade 2** events, treat with corticosteroids.
    - For **Grade 3-4** events, treat with systemic corticosteroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

6.6.2. Management of Infusion Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. **Table 6.6.2-1** shows treatment guidelines for

patients who experience an infusion-related reaction associated with administration of Cobolimab (TSR-022) and Dostarlimab (TSR-042).

Table 6.6.2-1: Infusion Reaction Management Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of study drug(s) with: • Diphenhydramine 50 mg po (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g.,	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids	No subsequent dosing

renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	• Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further trial treatment administration.	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration		

6.7. Subject Withdrawal/Discontinuation Criteria

Subjects are free to withdraw from the study at any time and without penalty or loss of future medical care, or any other benefits to which they are otherwise entitled. Subjects may discontinue study medication for any of the following conditions:

- Dose-limiting or other unacceptable toxicity considered to be related to study medication;
- Disease progression by RECIST v1.1;
- If, in the opinion of the Investigator, it is medically necessary;
- Subject withdraws consent for the study (note that subjects who withdraw consent for additional study treatment and procedures will continue to be followed for long-term
- Survival unless they explicitly withdraw consent for any follow-up);
- Subject develops an intercurrent illness or adverse event that precludes further participation, or requires a prohibited concomitant treatment;
- Subject becomes pregnant or begins breastfeeding;
- Subject is lost to follow-up.
- Investigator, Sponsor, GSK, or regulatory agency becomes aware of conditions of events that suggest a possible risk or hazard to participants if the clinical study continues;
- Termination of the trial.

Subjects discontinuing study medication earlier than planned or withdrawing from the study should undergo the subsequent End of Treatment (EOT) clinical and laboratory assessments as soon as possible after study medication is stopped and the requisite safety follow-up period of 30 days should also be followed. The reason for withdrawal will be recorded in the electronic case report form (eCRF) and the subject's source medical record. All subjects will continue to be followed every three months after the last Dostarlimab (TSR-042) or Dostarlimab (TSR-042)/Cobolimab (TSR-022) treatment for long-term survival follow-up until death, loss to follow-up, or withdrawal of consent for follow-up.

For participants who are thought to be lost to follow-up, at least 3 documented attempts, including 1 via certified mail, should be made to contact the participant before the participant is deemed lost to follow-up.

6.8. Subject Replacement Strategy

Subjects who receive at least 1 dose of Dostarlimab (TSR-042) or Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination are evaluable for safety.

Patients who complete pre-operative therapy and receive surgery will be evaluable for pathologic response rate and other efficacy endpoints.

Subjects who are non-evaluable for efficacy may be replaced.

6.9. Duration of Therapy and Follow Up

In the Pre-Operative Phase, a cycle is 3 weeks long, while in the Post-Operative Phase, a cycle is 6 weeks in length.

Pre-Operative Phase: 6 weeks (cycles 1-2).

Surgery and recovery: up to 6 weeks total.

Pre-Operative Phase: 48 weeks (cycles 3-10).

Details regarding safety, response and survival follow up are detailed in **Sections 10.7 to 10.9**.

6.10. Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

- Quality or quantity of data recording is inaccurate or incomplete
- Poor adherence to protocol and regulatory requirements
- Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

Plans to modify or discontinue the development of the study drugs. In the event of GSK's decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.11. Immune related Adverse Events of Interest and Guidelines for Management

AEs (both nonserious and serious) associated with Cobolimab (TSR-022) and Dostarlimab (TSR-042) exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment.

In general, Cobolimab (TSR-022) and Dostarlimab (TSR-042) must be withheld for drug-related Grade 3 toxicities, as well as for certain immune-related adverse events of interest (irAEIs), but may be resumed upon recovery to Grade ≤1; Cobolimab (TSR-022) and Dostarlimab (TSR-042) will be permanently discontinued for any drug-related Grade 4 AE. Cobolimab (TSR-022) and Dostarlimab (TSR-042) must be permanently discontinued for certain irAEIs as described in **Table 6.12-1**.

The specific immune-related AEs typically observed with anti-PD-1 antibodies will be managed according to the guidelines summarized below in **Table 6.12-1** (Costa et al., 2015).

Given the mechanism of action of Cobolimab (TSR-022) and Dostarlimab (TSR-042), it is anticipated that activation of cellular immune system can be manifested as immune-related AEs. Based on available safety data from checkpoint inhibitors, treatment related adverse events (TRAEs) with the specific grades listed below were selected as immune-related adverse events of interest (irAEIs). The list of irAEIs may be updated upon emerging data.

Refer to **Table 6.12-1** for details on the management of Cobolimab (TSR-022) and Dostarlimab (TSR-042) dose delays and discontinuation for specific irAEIs. Detailed guidance for the administration of rescue medications and supportive care are available below. For all irAEIs listed in **Table 6.12-1**, Dostarlimab (TSR-042) and/or Cobolimab (TSR-022) should be withheld until the patient is clinically and metabolically stable and AEs have resolved to Grade ≤1. If systemic steroids are used as a part of irAEI management, the total dose of daily steroids should be equal to or less than 10mg prednisone at the time of resuming Cobolimab (TSR-022) and Dostarlimab (TSR-042).

All treatment delays (including any missed doses) and discontinuations, and the reason for delays or discontinuation of Cobolimab (TSR-022) and Dostarlimab (TSR-042), should be documented.

Table 6.12-1: Guidelines for treatment of immune related AEs of interest.

Toxicity	**Withhold Treatment for AE Grade**	**Restarting Treatment/Discontinuation**
Diarrhea/colitis	2 to 3	Restart dosing when toxicity resolves to Grade 0 to 1.
	4	Permanently discontinue.
AST, ALT, or increased bilirubin	2 (AST or ALT > 3 and ≤ 5 × ULN or total bilirubin > 1.5 and ≤ 3 × ULN)	Restart dosing when toxicity resolves to Grade 0 to 1.
	3 or 4 (AST or ALT > 5 × ULN or total bilirubin > 3 × ULN)	Permanently discontinue (see exception below).[a]
T1DM or hyperglycemia	3 or 4 hyperglycemia or T1DM (associated with metabolic acidosis or ketonuria)	Restart dosing in appropriately managed, clinically and metabolically stable patients, insulin replacement therapy is required.
Immune-related encephalitis	Any grade	Permanently discontinue.

Toxicity	Withhold Treatment for AE Grade	Restarting Treatment/Discontinuation
Hypophysitis	2 to 4	For Grade 2 to 3 AEs, hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0 to 1. For recurrence or worsening of Grade ≥2 hypophysitis after corticosteroid taper has been completed and patient is on adequate hormone replacement therapy, permanently discontinue. For Grade 4 AEs, permanently discontinue.
Hyperthyroidism	3	Restart dosing when toxicity resolves to Grade 0 to 1.
	4	Permanently discontinue.
Infusion-related reaction	2[b]	Restart dosing when toxicity resolves to Grade 0 to 1.
	3 or 4	Permanently discontinue.
Pneumonitis	2	Restart dosing when toxicity resolves to Grade 0 to 1. If Grade 2 recurs, permanently discontinue.
	3 or 4	Permanently discontinue.
Rash	3	Restart dosing when toxicity resolves to Grade 0 to 1.
	4	Permanently discontinue.
Renal failure or nephritis	2	Restart dosing when toxicity resolves to Grade 0 to 1.
	3 or 4	Permanently discontinue.
Recurrence of AEs after resolution to Grade ≤1	3 or 4	Permanently discontinue.

6.12. Surgical Considerations

The team members will make every effort to comply with the surgical procedures within the time windows allowed in this study protocol. However, under certain circumstances and as discussed between the sub-investigator(s) and the principal investigator, an alteration in the surgical schedule/timing is allowed. These include (but are not limited to) the following:

- A 4 (up to; 3 weeks preferred) week window between the baseline biopsy and the first dose of Dostarlimab (TSR-042) or Dostarlimab (TSR-042)/Cobolimab (TSR-022) is allowed.
- The definitive surgery may be a distant lymphadenectomy, resection of in-transit metastases or resection of distant oligometastases, as clinically indicated. The definitive surgery may be divided into more than one surgical procedure, scheduled at different time points as clinically/surgically indicated. Under certain circumstances, the definitive surgery may be done after completion of additional therapy or earlier if Cobolimab (TSR-022) or Dostarlimab (TSR-042) were discontinued due to adverse events or other reasons. Tissue from any of these

surgical procedures may be banked under this protocol following the same protocol procedures for tissue handling and banking. The tissue for banking may be digested, frozen or handled in another alternative method as discussed with the investigator.

NOTE: The surgical guidelines are general and may be followed or modified at the discretion of the expert surgical oncologist on the case as clinically indicated and depending on the specifics of the individual surgical case.

For the baseline biopsy required on this study, patients will undergo a standard cutting needle technique, core needle, punch biopsy, open technique, or other technique at the discretion of the sub-investigator/investigator. The choice of specific surgical technique will be at the discretion of the surgeon or medical oncologist and actual techniques will be the same as those used as therapeutically or diagnostically indicated to surgically treat or confirm the clinical suspicion of recurrent or metastatic disease in any patient undergoing conventional evaluation and treatment (standard of care) within 21 days (preferred; and up to 4 weeks allowed) prior to entry to the study.

6.12.1. Excision of Primary Cutaneous Melanoma with Associated LN and/or Satellite/In-Transit Lesions

All patients with initial presentation of T1-4 melanoma will be treated by wide excision of the primary. Definitive surgery will include wide excision of the primary tumor and lymphadenectomy and/or resection of satellite/in-transit lesions (as appropriate). Recommended margins are a minimum of 1cm for lesions whose Breslow's thickness is ≤1 mm; and up to 2cm when anatomically feasible for lesions whose Breslow's thickness is >1 mm.

For patients with known primary cutaneous melanoma lesion and no history of wide local excision of that primary lesion, an adequate wide excision of the primary lesion (minimum margin 1 cm) is recommended. The wide local excision will be done at the time of complete lymphadenectomy.

Patients with nodal relapse after an inadequate primary excision will undergo wide excision at the time of complete lymphadenectomy.

For subungual melanoma, a distal interphalangeal amputation with histologically negative margins constitutes an adequate wide excision. The specimen shall be excised to include skin and all subcutaneous tissue down to the muscular fascia. Fascia may be included at the discretion of the operating surgeon. Closure of the defect may be via primary closure, split thickness skin graft, or rotation-flap at the discretion of the surgeon.

6.12.2. Regional Lymphadenectomy

All patients should undergo one of the following staging lymphadenectomies, as found surgically applicable by the treating surgical oncologist. **Note:** For patients undergoing sentinel node mapping and lymphoscintigraphic and dye lymphographic identification of regional nodal drainage, the minimum number of nodes may be less than the mandatory minimum numbers of 5/groin, 10/axilla, and 15/cervical node dissection.

6.12.2.1. Head/neck lesions

Face, ear and anterior scalp: Modified radical neck or radical neck dissection. Parotidectomy to be included if lymphoscintogram indicates flow to the area (to yield a minimum of 15 nodes).

Submandibular and anterior neck: Modified radical or radical neck dissection (to yield a minimum of 15 nodes).

Posterior scalp, posterior neck and uppermost trunk (areas that drain to posterior cervical triangle): Modified posterior triangle neck dissection with suboccipital nodes (to yield a minimum of 8 nodes).

6.12.2.2. Upper extremity lesions

Axillary node dissection will be performed per established guidelines. The pectoralis minor muscle may be divided or sacrificed at the surgeon's discretion.

6.12.2.3. Lower extremity lesions

Superficial inguinal node dissection will be performed per established guidelines. A deep inguinal node dissection will be at the discretion of the surgeon, but if performed, the established guidelines should be followed as closely as possible.

6.12.3. Lymphadenectomy for Nodal Recurrence

Regional node recurrences will be treated using the appropriate lymphadenectomy procedure. Whenever possible, diagnosis of regional node recurrence will be made using punch or open biopsy technique to provide baseline pathologic material needed for evaluation of treatment effect. At the time of the definitive lymphadenectomy, the biopsy site will be included in the operative specimen.

6.12.4. Resection of In-Transit and/or Satellite Lesions

For in-transit and/or satellite lesions, every effort should be made to identify and resect the draining lymph node(s).

There are no evidence-based data to support a particular peripheral margin of excision for in-transit/satellite metastases, and the wide local excision guidelines for a primary lesion do not apply. Minimum gross margins of 1cm are recommended at the discretion of the treating surgical oncologist.

Whenever possible, diagnosis of in-transit/satellite recurrence will be made using punch or core biopsy technique to provide baseline pathologic material needed for evaluation of treatment effect. At the time of the definitive surgery, the biopsy site will be included in the operative specimen.

6.12.5. Metastatectomy for Oligometastatic Lesions

Oligometastatic disease will be surgically excised with appropriate margins. If core biopsy was used to provide baseline pathologic material needed for evaluation of treatment effect, biopsy site will be included in the operative specimen at the time of the definitive surgery.

7. Response Assessment

7.1. Evaluating and Measuring Neoadjuvant Response in Melanoma

Neoadjuvant therapy in melanoma is an active area of investigation with numerous completed and ongoing trials studying a variety of therapeutic interventions utilizing diverse designs. Several agents in the melanoma armamentarium have been evaluated in the neoadjuvant context including: pembrolizumab (Huang et al., 2019), nivolumab (Amaria et al., 2018) and nivolumab/ipilimumab combination (Amaria et al., 2018; Blank et al., 2018; Rozeman et al., 2019). In earlier studies, response was typically assessed using chemotherapy criteria and reported as pathologic complete response (pCR) rates. In these studies, pCR was defined using residual viable tumor (RVT) derived from criteria from neoadjuvant studies of chemotherapy in select tumors including lung cancer (Pataer et al., 2012).

Neoadjuvant use of immuno-oncologic agents results in distinct histopathologic features compared to neoadjuvant chemotherapy. Specifically, neoadjuvant PD-1 therapy produces unusual features beyond CD8+ T cell infiltrate and tumor necrosis previously associated with response including features in areas adjacent to the actual tumor – a location termed "the regression bed" (Cottrell et al., 2018; Stein et al., 2019). Histopathologic features associated with response herein include neovascularization; proliferative fibrosis; presence of cholesterol clefts; development of tertiary lymphoid structures; presence of plasma cells, giant cells, foamy macrophages and granulomas (Cottrell et al., 2018; Tetzlaff et al., 2018; Stein et al., 2019).

Cognizant of the different mechanism of action of immuno-oncologic agents, more recent studies have utilized alternative means of assessing response using novel immuno-oncologic agent-specific criteria (Cottrell et al., 2018; Tetzlaff et al., 2018; Stein et al., 2019). In these methods, RVT (%RVT) is defined as the total surface cross - sectional area of RVT divided by the total tumor bed area (comprising RVT area + areas of necrosis) (Cottrell et al., 2018; Tetzlaff et al., 2018). Using these criteria, the following agreed upon standard definitions of pathologic response are:

- Pathologic complete response (pCR): 0% RVT; absence of viable tumor cells in the surgically resected post-treatment specimen.
- Pathologic near-complete/major response (pMR): <0 to ≤10% RVT; that is, near-complete absence of viable tumor cells in the surgically resected post-treatment specimen
- Pathologic partial-response (pPR): >10% RVT but ≤50% RVT.
- Pathologic non-response (pNR): >50% RVT; >50% viable tumor in the surgically resected post-treatment specimen.

In this study, pathologic response will be reported as follows:

- Sections reveal completely regressed/partially viable/mostly viable melanoma involving __ of __ lymph nodes or fibroconnective tissue.
- Overall tumor response (pathologist to indicate)
    - Complete pathologic response (0% RVT)
        - Yes
        - No
    - Major pathologic response (≤10% RVT)

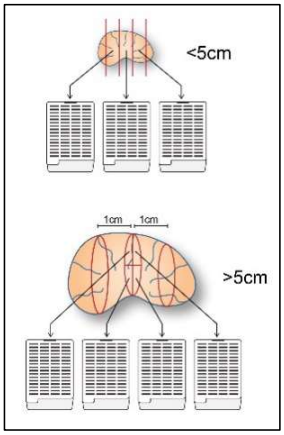
        - Yes
        - No
    - Pathologic partial response (<10 to ≤50% RVT)
        - Yes
        - No
    - Pathologic non-response (>50% RVT)
        - Yes
        - No
- An evaluation of the completely treated tumor bed reveals:
    - Viable tumor: Present/Not identified
        - Extent: __%
    - Tumoral melanosis: Present/Not identified
        - Extent: __%
    - Tumoral necrosis: Present/Not identified
        - Extent: __%
    - Fibrosis: Present/Identified
        - Extent: __% of the tumor bed occupied by fibrosis
        - Hyalinized: __%
        - Proliferative: __%
    - Inflammatory infiltrate: Present/Not identified
        - Extent: __% and Composition

In order to achieve accurate and reproducible pathologic assessment in neoadjuvant treated specimens, the following requirements for the gross assessment and submission of tissue following neoadjuvant treatment as recommended by the International Neoadjuvant Melanoma Consortium (see figure below):

- If the largest grossly positive lymph node/tumor measures ≤5 cm in greatest dimension, then the entire lymph node/tumor should be entirely submitted at 2 mm serially sectioned intervals.
- For any grossly positive lymph node/tumor measuring >5 cm in greatest dimension, then representative sections of the largest lymph nodes may be utilized to avoid oversampling as indicated below.
    - Following serial sectioning of each lymph node, for those grossly positive nodes > 5 cm, sections representing a complete cross section of the entire surface area should be submitted per 1 cm of each grossly positive lymph node.
    - All lymph nodes < 5cm in specimens where the largest node(s) exceeds 5 cm should be submitted entirely.

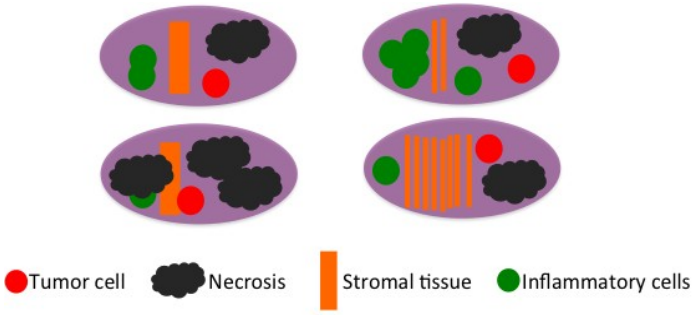
Figure 3: Methods of Assessing %RVT In Patients Receiving Neoadjuvant Therapy

Step 1:
Serial sections depending on size of tumor/LN:
- Largest grossly positive lymph node/tumor measures ≤5 cm
- Largest grossly positive lymph node/tumor measures >5 cm



Step 2:
Assessment:
- ≤5 cm: submit entire LN/tumor at 2mm serial sections
- **>5 cm: submit representative sections**
  - **Complete sections from LN/tumor <5cm**
  Representative sections from LN/tumor >5cm

Step 3:
1. **Calculate residual viable tumor (RVT) = total surface area of RVT**
2. **Calculate total tumor bed area = total area of regression + RVT + necrosis**



Step 4:
- **%irRVT = total RVT/total tumor bed area x 100**
- **Each surgical sample will be scored by the initial reading pathologist and independently by 3 blinded pathologists**
- **Final irRVT is the mean score of 3 independent reads**
- **%irRVT for each sample will be reported as mean +/-SD**

Adapted from Tetzlaff et al (Ann Oncol 2018), Cottrell et al (Ann Oncol 2018)

Other information required for the case assessment by the local pathologist include:

- Patient information: subject ID, nature of surgery, local pathology accession number (including sub-parts), total number of slides examined, date of review

All cases will undergo central pathology review. The following information is required for the case assessment by the central pathologist:

- Patient information: subject ID, nature of surgery, local pathology accession number (including sub-parts), total number of slides examined, date of review
- Digitized and/or manual slides of entire case.

This is summarized in **Appendix B (Pathology Specimen Processing for Neoadjuvant Melanoma Study (Neo-Mel-T) and Appendix C): Specimen Processing and Case Report Form for Pathologic Response Assessment.**

7.2. Radiographic Response Assessment in Solid Tumors

For the purposes of this neoadjuvant study, radiographic response is a secondary endpoint.

In the Pre-Operative Phase, all patients will be re-evaluated for response after completion of the Pre-Operative Phase at weeks 6-10. During Pre-Operative Phase, confirmatory scans for tumor response or progression are not required. Guidelines regarding nature and timing of imaging studies are delineated in **Section 10.11**.

In the Post-Operative Phase, all patients will be evaluated for relapse every 9 weeks. Guidelines regarding nature and timing of imaging studies are delineated in Section 10.11. During this phase, patients with disease progression (PD) should have a scan confirming PD 4-6 weeks following the initial scan showing RECIST v1.1 defined PD. Furthermore, investigators should make every effort to biopsy areas of suspected progression to confirm this prior to determining PD.

Following completion of therapy at EOT (or at the time of study drug discontinuation), participants who have not developed progressive disease, will enter Post-Treatment Surveillance ~12 weeks after last on-treatment time point. Post-Treatment Surveillance will continue till 15 years from study entry. During this phase, all patients will be evaluated for relapse. Guidelines regarding nature and timing of imaging studies are delineated in **Section 10.11**.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer et al., 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in RECIST v1.1.

The following general principles must be followed:

- To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.
- Measurable disease is defined by the presence of at least one measurable lesion.
- All measurements should be recorded in metric notation by use of a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

8. Trial Flow Chart

Procedure/Assessment	**Screening (Days -28 to 0)[A]**	**Pre-Operative Phase**			**Pre-Surgical Assessment and Surgery**	**Post-Operative Phase**	**End of Treatment[B]**	**30-Day Safety Follow Up[C]**	**Post-Treatment Surveillance[D]**
		Week 0	**Week 3**	**Week 6**	**Weeks 6-10**	**Week 10 and Onwards**			
Visit Windows		**+/- 3 days**	**+/- 3 days**	**+/- 3 days**		**+/- 1 week**	**+/- 1 week**	**+/- 1 week**	**+/- 14 days**
Pre-op phase: Dostarlimab (TSR-042) or Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination dose number[E]		Cycle 1	Cycle 2			Cycles 3-10			
Post-op phase: Dostarlimab (TSR-042) dose number[E]						Cycles 3-4 (500mg q3, 4 doses) Cycles 5-10 (1000mg q6, 6 doses)			
Pre-treatment tumor biopsy[F] (biopsy at progression is optional)	X								
Planned surgical evaluation[G]	X								
Surgical resection and pathological response assessment[H]					X				
Exploratory biomarker analyses[I]	X		X	X	X (2 tubes only; PBMC)	X (every 6 weeks starting with 1st	X		

						maintenance cycle)			
Stool sampling[J]	X		X	X		X (every 6 weeks starting with 1st maintenance)	X		
Dietary history questionnaire[K]	X								
Informed consent	X								
Eligibility criteria assessment	X								
Medical history, demographics, cancer history including prior cancer medications	X								
Physical exam[L]	X	X	X	X		X	X	X	
Clinical laboratory tests (hematology, serum chemistry, other chemistry, urinalysis, coagulation tests and thyroid function)[M]	X	X	X	X		X		X	
Disease assessment[N]	X				X (prior to surgery)	X (every 9 weeks starting with cycle 4)		X	

Study Calendar Notes:

[A]Screening period is 28 days prior to first dose.

- During **Screening**, MRI brain with contrast (or CT equivalent) should be performed to exclude CNS metastatic disease. CNS imaging need not be repeated on study unless patient is symptomatic.

[B]End-of-treatment (**EOT**) assessments to be performed within 7 days following removal of subject from treatment. Removal of a subject from treatment is defined as the time in which the Investigator decides to discontinue Dostarlimab (TSR-042) or Dostarlimab (TSR-042)/Cobolimab (TSR-022) treatment for a subject.

- Management of patients who develop unacceptable toxicity is defined in **Section 6.6.1.**
  - Patients who develop unacceptable toxicity deemed related to Cobolimab (TSR-022) but not Dostarlimab (TSR-042), may continue Dostarlimab (TSR-042) after Cobolimab (TSR-022) discontinuation for duration as defined in **Section 6.6.1.**
  - Patients who develop unacceptable toxicity deemed related to Dostarlimab (TSR-042) must discontinue study therapy.
- Details of EOT assessments are in **Section 10.6**.

[C]**Safety Follow Up** visits to be performed 30 days after last dose of protocol therapy or prior to initiation of a new cancer therapy (whichever is appropriate).

- See **Section 10.7** for details.

[D]**Post-treatment surveillance**

- This phase begins upon completion of 30 Day Follow Up.
- Procedures to be followed during this phase are outlined in **Section 10.8** and will include imaging (CT or PET/CT), laboratory studies (CBC, CMP, LDH) and any other studied (thyroid function etc.) as deemed necessary at the discretion of the treating physicians and according to established Standard of Care.

[E]Dostarlimab (TSR-042) or Dostarlimab (TSR-042)/(Cobolimab (TSR-022) combination is dosed as outlined in **Section 6.1.2.**

- Vital sign monitoring
  - Pre-Operative Phase: vital signs are to be collected at least 30 minutes prior to Dostarlimab or Dostarlimab/Cobolimab (TSR-022) infusion, and at 30 (±15) minute intervals for 1 hour following each cycle.
  - Post-Operative Phase: vital signs are to be collected at least 30 minutes prior to Dostarlimab and at 30 (±15) minute intervals for 1 hour following each cycle.
  - Infusions will be administered where resuscitation equipment is readily available.
- Dosing schedule
  - Pre-Operative phase: each cycle is 3 weeks long.
  - Post-Operative phase: each cycle is 6 weeks long.

[F]Tumor biopsy must be performed prior to commencing treatment. Other collection time points are the day of resection and is optional at the time of disease progression;

- Tumor biopsy must be of lesion that is planned for resection.
- Punch, core (>4 18gauge) and/or surgical biopsies are acceptable.
- If core biopsy is performed, pathology confirmation is **required** to ensure adequate tissue is obtained.

[G]Assessment of planned resectability must be made DURING screening.

- Planned surgery after Pre-Operative Phase must be with surgeon who initially made determination of planned resectability.
- Extent of surgery to follow guidelines in **Section 6.13**.

[H]Surgical specimen processing

- Surgical specimen processing and pathological response determination are outlined in **Section 7.1** and **Appendices B** and **C.**
- Further instructions are detailed in the attached **Laboratory Manual**.

[I]Exploratory biomarker blood samples are to be collected at the following times:

- PBMC: screening; W3D1; W6D1; pre-surgery (day of surgery, only 2 tubes); every 6 weeks starting with 1st maintenance cycle (Cycle 4, ~W10D1); EOT.
- Plasma and serum: screening; W3D1; W6D1; every 6 weeks starting with 1st maintenance cycle (Cycle 4, ~W10D1); EOT.
- ctDNA in Streck tubes: screening; W3D1; W6D1; pre-surgery; every 6 weeks starting with 1st maintenance cycle (Cycle 4, ~W10D1); EOT.

[J]Exploratory biomarker stool samples are to be collected at the following times:

- Screening; W3D1; W6D1; every 6 weeks starting with 1st maintenance cycle (Cycle 4, ~W10D1); EOT.

[K]Dietary history questionnaire (**Appendix A**) will be performed at **Screening only**.

[L]A full physical exam will be conducted at screening, each treatment visit and **EOT**.

- Screening physical exam may be performed up to 72 hours prior to the Week 0 Day 1 visit. If the full physical exam is performed >72 hours prior to the Week 0 Day 1 (W0D1) visit, then a brief (symptom directed) physical exam must be performed within 72 hours prior to initiation of TSR-042 or TSR-042/Cobolimab (TSR-022) combination.
- Physical exams should include assessment of ECOG performance status; and weight.
- Heights will be obtained at Screening.

[M]Clinical laboratory tests may be performed up to 72 hours prior to Dostarlimab (TSR-042) or Dostarlimab (TSR-042)/Cobolimab (TSR-022) administration. Details in **Section 10.10**.

- Pregnancy testing should be performed at Screening, every 12 weeks while on protocol therapy, and at Safety Follow-up visit. See **Section 10.10** for details.
- Thyroid tests should be performed at Screening, C2D1, and then every 6 weeks while on protocol therapy.
- Partial thromboplastin time (PTT) and prothrombin time/international normalized ratio (INR) tests should be at Screening only. There is no need to repeat these unless otherwise indicated (concomitant anticoagulation etc).
    - Coagulation parameters may need to be repeated prior to surgery at the discretion of the treating **surgical oncologist**.

[N]CT or PET/CT scans to assess tumor status will be obtained at the following intervals (baseline value should be performed ≤4 weeks prior to first dose of study therapy).

- Screening; pre-operatively; and repeated every 9 weeks starting with Cycle 4 (during Post-Operative Phase).
- Details regarding baseline, pre-operative and restaging scans are delineated in **Section 10.11**.
- It is ideal for the patient to have the same imaging study performed throughout the study (screening PET/CT, pre-surgery PET/CT, post-operative phase PET/CT; OR screening contrast-enhanced CT, pre-surgery contrast-enhanced CT, post-operative phase contrast-enhanced CT).

Note: The Investigator/Sub-Investigators are expected to make every reasonable effort to comply with the study calendar. However, if a cycle is missed or a subject's study treatment and/or testing days need to be rescheduled due to the subject's inability to comply with the study calendar (i.e., hospitalizations, business and vacation travel plans, illness, transportation issues, holidays, family emergencies, etc.), a window of ± one week is available for rescheduling of study treatment and procedures per the discretion of the Sub- Investigator, and as discussed with the Investigator.

9. Pharmaceutical Information

9.1. Dostarlimab (TSR-042)

The Trial Flow Chart (**Section 7.0**) summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

9.1.1. Identity

Dostarlimab (TSR-042) is an IgG4 antibody and will be supplied as a solution in vials containing 500 mg (50 mg/ml, respectively).

9.1.2. Potential Risks

As of January 2020, dostarlimab has been studied in about 1000 patients with advanced or recurrent solid tumors in clinical trials, with just under one-half of these patients receiving dostarlimab in combination with other medicines. As with any research studies, the study treatment and study procedures involve known and unknown risks and side effects. Any medication may have temporary and/or permanent side effects. Some of the side effects mentioned below can be life-threatening or fatal.

Very common side effects include anemia, nausea, vomiting, diarrhea, pruritus, rash, AST increased, ALT increased, and transaminases increased.

Common side effects include adrenal insufficiency, hypothyroidism, hyperthyroidism, pneumonitis, colitis, myalgia, chills, fever, increase in blood creatinine, hypokalemia, infusion related reactions which can occur within 24 hours after receiving an intravenous infusion, or which can be delayed for up to about 2 weeks and may resemble serum sickness. Infusion-related reactions may include dizziness or fainting, flushing, rash, fever, chills, shortness of breath, increased or decreased blood pressure, increased heart rate, swelling of the lips, tongue or face, feeling sick to your stomach, back pain or pain at the site of infusion. Although infusion-related reactions are usually reversible, they can be severe or life threatening and redness, itching, swelling or pain around the injection site.

Uncommon risks include autoimmune haemolytic anemia, thyroiditis, hypophysitis, diabetic ketoacidosis, type 1 diabetes mellitus, uveitis, hepatitis, pancreatitis, polymyalgia rheumatica, nephritis and thyroiditis.

There are rare but serious immune-related adverse events which have been seen when dostarlimab was used in combination with other medications: myositis, systemic inflammatory response syndrome and hemophagocytic lymphohistiocytosis.

There may be other risks with dostarlimab called class effects. They are potential risks but not known as side effects for dostarlimab so far. The most significant class related side effects are “immune-related”, which can affect multiple organs of the body including gastrointestinal tract, endocrine system, cardiovascular system, lungs, liver, skin, musculoskeletal system and nervous system.

There is the potential for human anti-drug reactions to Dostarlimab (TSR-042) or hypersensitivity reactions. If these effects occur, whether acute or delayed, they may vary in severity from mild rash to severe anaphylaxis, and they may be life threatening. Patients should be monitored for such effects and emergency treatment must be available for promptly treating patients with immune reactions during infusions. As Dostarlimab (TSR-042) only has limited human experience, the investigator should be alert for other AEs, including idiosyncratic reactions.

9.1.3. Packaging, Labeling and Storage

Dostarlimab (TSR-042) for infusion is supplied in vials containing 500 mg at a concentration of 50 mg/mL.

9.1.4. Dispensing

The investigator agrees that study drug(s) will be dispensed by the investigator or sub-investigator(s) named on the Investigator Agreement or their qualified designees. The investigator, sub-investigators, or qualified designees also agree that the study drug(s) will be dispensed only to study subjects who have provided written informed consent and have met all entry criteria and in accordance with the instructions provided in the storage and handling manual.

9.1.5. Disposal and Destruction

Dostarlimab (TSR-042) should be destroyed at the investigational site if permitted by local regulations.

9.2. Cobolimab (TSR-022)

9.2.1. Identity

TSR-022 is a TIM-3 binding humanized monoclonal IgG4 antibody and will be supplied as a solution in vials containing 160 mg (20 mg/mL).

9.2.2. Potential Risks

The potential risks of Cobolimab (TSR-022) are based on limited clinical experience. The most commonly reported AEs were fatigue, abdominal pain, nausea and vomiting

9.2.3. Packaging, Labeling and Storage

Cobolimab (TSR-022) for infusion is supplied in vials containing 160 mg at a concentration of 20 mg/mL. The label text of the study treatment will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries. The study treatment will be open-label and non-patient-specific. Study Drug will be labeled in accordance with local regulatory requirements.

9.2.4. Dispensing

The investigator agrees that study drug(s) will be dispensed by the investigator or sub-investigator(s) named on the Investigator Agreement or their qualified designees. The investigator, sub-investigators, or qualified designees also agree that the study drug(s) will be

dispensed only to study subjects who have provided written informed consent and have met all entry criteria and in accordance with the instructions provided in the storage and handling manual.

9.2.5. Disposal and Destruction

Cobolimab (TSR-022) should be destroyed at the investigational site if permitted by local regulations.

10. Schedule of Assessments

10.1. Schedule of Assessments

The Trial Flow Chart in summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or GSK for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

10.2. Treatment Period

The study consists of 3 main phases:

- **Pre-Operative Phase (Weeks 0-6):**
  - Either Dostarlimab (TSR-042) monotherapy or Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination therapy will be administered.
  - Dostarlimab (TSR-042) only arm: Dostarlimab (TSR-042) 500mg Q3W for 2 cycles (on W0D1, W3D1, cycles 1-2).
  - Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination arm: Cobolimab (TSR-022) 300mg Q3W and Dostarlimab (TSR-042) 500mg Q3W for 2 cycles (on W0D1, W3D1, cycles 1-2). During this period, missed doses will not be made up.
- **Pre-surgical assessment and surgery:**
  - Restaging imaging will be obtained.
  - Any pre-operative evaluation deemed necessary per surgical oncologist.
  - Definitive surgery as delineated in **Section 6.13**.
- **Post-Operative Phase (48 Weeks):**
  - Dostarlimab (TSR-042) monotherapy will be administered every 3 weeks for 4 doses, and then every 6 weeks for 6 doses (W12D1 onwards).
    - Cycles 3-4: Dostarlimab (TSR-042) 500mg Q3W for 4 doses.
    - Cycles 5-10: Dostarlimab (TSR-042) 1000mg Q6 weeks for 6 doses. During this period, missed doses will be made up.

10.3. Screening

Screening starts with the subject's provision of a written informed consent and should be completed at least 28 days prior to initiation of study drug(s). During this period, the

procedures/tests as outlined in the Study Flow Chart in Section 7.1 must be completed including:

- Pre-treatment tumor biopsy.
- Surgical evaluation.
- Laboratory assessments as outlined in **Section 10.10**.
- Radiologic tumor assessments as outlined in **Section 10.11**.

During screening visit, study investigator (or designee) must discuss the following with patients:

- Inclusion and exclusion criteria.
- Medical history – pertinently any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator.
- Prior and concomitant medications. All medications related to reportable SAEs and ECIs should be recorded as defined in **Section 11**.
- Disease details and treatments.

10.4. Cycle 1 and Subsequent Cycles

During each treatment visit, study investigator (or designee) must perform the following assessments on each subject.

- Adverse event (AE) monitoring
    - The study investigator (or designee) will assess each subject to evaluate for potential new or worsening AEs and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.
    - All AEs of unknown etiology associated with Dostarlimab (TSR-042) or Cobolimab (TSR-022) exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See **Section 11** regarding the identification, evaluation and management of AEs of a potential immunological etiology.
    - Related and clinically significant AEs occurring within 30 days after the last dose of study drug should be recorded. Patients who are discontinued from the study due to an unacceptable drug-related AE will be followed until the resolution of the AE to Grade 0-1 or stabilization or until initiation of a new therapy for their cancer, whichever occurs first. Related SAEs that occur within 90 days of the end of treatment or before initiation of a new antineoplastic treatment should also be followed and recorded.
    - Please refer to **Section 11** for detailed information regarding the assessment and recording of AEs.

- Full physical exam
    - The study investigator (or designee) will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history.
- Vital signs
    - The study investigator (or designee) will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (**Section 8**). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure.
- Eastern Cooperative Oncology Group (ECOG) performance scale
    - The study investigator (or designee) will assess ECOG status according to Appendix A at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart (**Section 8**).

10.5. Surgery

Surgery will be performed as outlined in **Section 6.12**.

10.6. End of treatment (EOT)

For participants who complete all scheduled cycles of therapy, the EOT visit will be the same visit as the last scheduled and completed on-treatment visit, and will be the start of the safety follow-up period. For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on treatment visit (with all available safety and response data), and will not need to be repeated. Accordingly, for these participants, this visit will be considered the start of the safety follow-up period.

10.7. 30-Day Safety Follow-Up

The mandatory 30-Day Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

10.8. Post-Treatment Surveillance

All participants who have not developed progressive disease at the time of the EOT visit or at the time of study drug discontinuation, will enter Post-Treatment Surveillance ~12 weeks after last on-treatment time point.

These patients will continue to have radiologic (CT vs. CT/PET vs. PET at the discretion of the treating physician), laboratory studies (CBC, CMP, LDH) and clinical tumor assessments at the intervals directed below following the last dose of study drug, or until disease progression and/or withdrawal of study consent:

- Every 3 months (±2 weeks) if patient is <2 years from study entry.

- Every 6 months (±12 weeks) if patient is 2-5 years from study entry.
- Every 12 months (±12 weeks) if patient is > 5 years from study entry for up to 15 years.

Radiological assessments for participants who have ongoing clinical benefit will be collected for participants on the Post-Treatment Surveillance period of the study.

Participants who have disease progression following an initial course of study therapy **will** be allowed to receive other tumor directed therapy as required and **will not** be evaluated for response beyond the EOT visit. However, they will be followed to assess survival at a minimum of every 6 months up to year 5 following the last dose of study drug, or until disease progression/withdrawal of study consent.

10.9. Survival Follow-Up

Patients who have progressed (are no longer being followed for response) will continue to be followed for survival. Patients who have progressed may receive any therapy as directed by their treating physician. These patients will be followed either in person or telephone every 3 months (from EOT) for years 1-2, every 6 months for years 3-4 and annually thereafter until death, loss to follow-up, or withdrawal of consent. Duration of Survival Follow-Up will be for up to 15 years from study entry.

10.10. Laboratory Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory tests for hematology, chemistry, urinalysis, and others are specified in **Table 10.10-1**.

Laboratory tests for screening should be performed within 14 days of registration. After W0D1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Laboratory test results must be reviewed by the study investigator (or designee) and found to be acceptable prior to each dose of trial treatment.

Table 10.10-1: Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Platelet count WBC (total and differential including absolute neutrophil count)	Albumin Alkaline phosphatase Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Bilirubin (total; directly only if total is elevated above ULN) Total protein Blood urea nitrogen Bicarbonate Calcium Chloride Creatinine Glucose Potassium Sodium Lactate dehydrogenase (LDH) Uric acid	pH Specific gravity Glucose Protein Blood Nitrites WBCs Microscopic battery (RBCs, WBCs, epithelial cells, casts) - only if significant positive findings on urinalysis	Serum pregnancy test (β-human chorionic gonadotropin)[+] aPTT and PT (INR)[@] Thyroid function studies* [thyroid stimulating hormone (TSH) and free T4] HIV[$] Hepatitis B surface antigen (HBsAg) and surface antibody HBsAb)[$] Hepatitis C RNA (HCV RNA)[$]

[+] Perform on women of childbearing potential at Screening, every 12 weeks during protocol therapy and at Safety Follow-up Visit.
@Perform at Screening only; no need to repeat these unless otherwise indicated (concomitant anticoagulation etc).
[$]HIV, hepatitis B/C studies will be performed at Screening only when medically indicated by history and physical examination.
*Thyroid function studies required at screening, every 6 weeks during protocol therapy and at Safety Follow-up visit.

10.11. Tumor Imaging and Disease Assessment

Acceptable imaging studies to evaluate disease at baseline include:

- Contrast-enhanced CT scan of neck, chest, abdomen and pelvis (and affected body part if needed) (preferred)
- Whole body PET-CT scan (except brain)
- Brain imaging is to done only at Screening and need not be repeated unless clinically indicated. For brain imaging an contrast enhanced MRI is ideal. If an MRI of the brain cannot be done (or is contra-indicated) a contrast enhanced CT of the brain is acceptable.

Acceptable imaging studies to evaluate disease prior to surgery include:

- Contrast-enhanced CT scan of neck, chest, abdomen and pelvis (and affected body part if needed) (preferred)
- Whole body PET-CT scan (except brain)
- This study must be performed following week 6 but prior to definitive surgery.

Acceptable imaging studies to evaluate disease during Post-Operative Phase include:

- Contrast-enhanced CT scan of neck, chest, abdomen and pelvis (and affected body part if needed) (preferred)
- Whole body PET-CT scan (except brain)
- Studies will be performed every 9 weeks (-/+ 2 weeks) starting with week 15.
- It is ideal for the patient to have the same imaging study performed throughout the study (screening PET/CT, pre-surgery PET/CT, post-operative phase PET/CT; **OR** screening contrast-enhanced CT, pre-surgery contrast-enhanced CT, post-operative phase contrast-enhanced CT).

Additional staging studies will be done as clinically indicated at the discretion of the treating physician.

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST v.1.1).

10.12. Tumor Tissue Collection and Other Correlative Studies

Planned correlative analyses will include flow cytometric analyses of tumor samples, TIL and peripheral blood mononuclear cells (PBMC), IHC analyses of pre-/post- treatment tumor samples, tumor whole exome/RNA sequencing. Single-cell RNA sequencing will be performed on a subset of treated patients. Studies will be performed under the direction of the Principle Investigator along with co-Investigator Hassane Zarour.

Samples to be collected are outlined below in **Table 10.12-1**.

	Screening (Day -28 to -1)	Pre-Operative Week 0 Day 1 (Cycle 1 Day 1)	Pre-Operative Week 3 Day 1 (Cycle 2 Day 1)	Pre-Operative Week 6 Day 1 (Restaging Scan Review)	Surgery	Post-Operative every 9 weeks starting with Week 12 Day 1 (W12D1; W21D1; … ; W57D1)	EOT or Discontinuation
Assay 1: PBMC	X		X	X	X (only 2 tubes)	X	X
Assay 2: Cytokines and chemokines	X		X	X		X	X
Assay 3: Streck cfDNA (2 tubes)	X		X	X		X	
Assay 4: Whole Blood gDNA	X					X	
Assay 5: Tumor tissue	X				X		
Assay 6: H&E slides, pathology report and operation report	X				X		
Assay 7: Stool	X		X	X		X	X
Assay 8: Dietary History Questionnaire	X						

Table 10.12-1: Tumor, Blood and Biospecimen Collection

10.12.1. Tumor tissue

Tumor tissue will be processed as delineated in the laboratory manual.

10.12.2. Blood biospecimens

Blood biospecimens will be collected as outlined in the Laboratory Testing Schedule (see **Table 10.12-1**) and processed as delineated in the laboratory manual. Each tube must be clearly labeled to include:

- Protocol number
- Patient number
- Patient initials
- Originating institution/investigator name
- Date and time drawn
- Collection time point

10.12.3. Withdrawal and discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events

which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in **Section 11**. The schedule for Post-Treatment Visits including End of Treatment Visits and Follow-up Visits (Safety, Response and Survival) are delineated in Study Flow Chart (**Section 8**) and **Sections 10.6 to 10.9** respectively.

11. Adverse Event (AE), Serious Adverse Event (SAE) and Serious Unexpected Adverse Events (SUSAE)

11.1. Definitions

An **AE** is an untoward or medical occurrence associated with the use of study drug (active or placebo drug, biologic, or device) in clinical investigation subjects, which does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended symptom, sign, disease or condition, or test abnormality whether or not considered related to study drug. AEs that do not meet the definition for an SAE are considered non-serious AEs. AEs include:

- Changes described by the subject or signs observed by the Investigator or medical staff.
- Test abnormalities (i.e., laboratory tests, ECGs) that result in an alteration in medical care (diagnostic or therapeutic).

Disease progression is not considered an AE in this study.

Abnormalities present at baseline are considered AEs only if they reoccur after resolution or they worsen during the study.

An **SAE** is any **AE** that fulfills one of the criteria outlined in **Table 11.1-1**.

Table 11.1-1: Criteria for Determination of Serious Adverse Events

Death	An AE that results in death. *In this study, deaths that are unequivocally due to Disease Progression are **not** to be reported as SAEs.
Life-threatening AE	An AE that places the subject, in the view of the Investigator, at immediate risk of death from the AE as it occurred (i.e., does not include an AE that had it occurred in a more severe form, might have caused death).
Required or prolonged inpatient hospitalization	An AE that results in an initial inpatient hospitalization or prolongs an existing hospitalization of the subject. If a subject is hospitalized as part of the clinical use of the study drug, a period of normal hospitalization will be outlined in the protocol or by the judgment of the Investigator. Hospitalizations longer than this period will be prolonged hospitalizations.
Persistent or significant disability/incapacity	An AE that results in a substantial disruption of a subject's ability to conduct normal life functions.
Congenital anomaly/birth defect	A congenital anomaly/birth defect that occurs in the offspring of a subject exposed to the study drug.
Important medical event	An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above.

Examples of such "important 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.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as with important medical events described above.

Events that meet SAE criteria must be recorded and reported regardless of expectedness or assessed association with study drug.

Note: Planned hospital admissions or surgical procedures for elective procedures or for an illness or disease that existed before the signing of the ICF or before the subject was enrolled in the study will not be captured as SAEs. If planned admissions or procedures occur at a time other than what was planned (i.e., due to an exacerbation in the preexisting illness or disease), they should be reported as SAEs.

11.2. Evaluation of AE and SAE

The Investigator or designee is responsible for making an assessment as to the severity/grade (as defined in **Section 11.2.1** below), causality/relationship (as defined in **Section 11.2.2** below), and outcome of AEs and SAEs (as defined in **Section 11.2.3** below). In addition, the Investigator or designee must report any actions taken as a result of an AE or SAE.

11.2.1. AE severity and grade

For each recorded AE or SAE, the Investigator or designee must make an assessment of Grade using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade refers to the severity of the AE. Note that severity is not the same as "seriousness". Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

11.2.2. Causality and relationship to study drug(s)

For each AE or SAE, the Investigator will determine whether there is a reasonable possibility demonstrated by evidence that suggests a causal relationship between the study drug regimen (Dostarlimab (TSR-042) monotherapy or Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination), and the AE according to the categories provided in **Table 11.2.2-1**. Attribution of adverse events may be challenging particularly in patients receiving Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination. In patients receiving Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination, the relationship to either study drug (or the combination) should be based on careful attribution.

An AE with causal relationship not initially determined will require follow-up to assign causality which must be made by the Investigator prior to completion of the study. The Investigator may change his/her opinion of causality in light of follow-up information; if this occurs, the Investigator must amend the AE or SAE information accordingly.

Table 11.2.2-1: Classifications for Adverse Event Causality/Relationship

Classification	Definition
Unrelated	There is no suspicion of a causal relationship between exposure to the study drug regimen and the AE; another cause of the AE has been identified, no temporal association with study drug has been identified, or the study drug cannot be implicated.
Unlikely related	There is only a temporal relationship to study drug, but not a reasonable causal relationship between the investigational product and the AE.
Possibly related	There is some evidence supporting the possibility of a causal relationship between study drug regimen exposure and the AE; an alternative explanation (i.e., concomitant drug or concomitant disease) is inconclusive, the temporal association with study drug is reasonable, and the causal relationship cannot be excluded.

Probably related	An adverse event that has a timely relationship to the administration of the investigational drug regimen and follows a known pattern of response, but for which a potential alternative cause may be present.
Definitely related	There is strong evidence that there is a causal relationship between study drug regimen and the AE; the AE cannot be reasonably explained by an alternative explanation (i.e., concomitant drug or concomitant disease) and the temporal association with study drug is suggestive of a causal relationship.

An AE is considered related to Dostarlimab (TSR-042) monotherapy or Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination if the attribution is "possibly related", "probably related", or "definitely related".

11.2.3. Classification of AE outcome

Adverse event outcome describes the status of the AE at the last observation. The Investigator will document the outcome of each AE or SAE using the categories provided in **Table 11.2.3-1**.

Table 11.2.3-1: Classification for Adverse Event Outcome

Classification	Definition
Fatal	Termination of life as a result of an AE.
Not recovered/not resolved	Subject has not recuperated or the AE has not improved.
Recovering/resolving	Subject is recuperating or the AE is improving.
Recovered/resolved	Subject has recuperated, the AE resolved, or returned to baseline status / stabilized.
Recovered/resolved with sequelae	Adverse event has resolved, but the subject has been left with symptoms or pathology.
Unknown	Not known, not observed, not recorded, or refused.

11.2.4. Action taken regarding AE

The Investigator will provide the action taken regarding study drug in response to the AE. Classifications for each of the potential actions taken are provided in **Table 11.2.4-1**. More than one option may apply to a single AE/SAE. For example, study drug may be delayed and the dose reduced in response to an AE.

Table 11.2.4-1: Classifications for Actions Taken Regarding an Adverse Event

Classification	Definition
Dose not changed	No change in administration of study drug
Study drug interrupted	Temporary interruption (termination) in administration of the study drug
Study drug withdrawn	Administration of the study drug terminated (no further dosing)
Not applicable	Determination of a value is not relevant in the current context
Unknown	Not known, not observed, not recorded, or refused

11.3. Timeframe for AE/SAE Collection

The Investigator is required to record all AEs occurring during the clinical study (21 CFR 312.64[b] and ICH E6 [R1]) starting from the date of first dose of study drug(s) until 30 days after the last dose of Dostarlimab (TSR-042) monotherapy or Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination on the AE page of the eCRF. SAEs that are considered possibly related to study drug and occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. SAEs as defined in **Section 11.1** must also be reported to the Sponsor (UPMC) or its representative within 24 hours of knowledge of their occurrence, in accordance with **Section 11.5.1**.

11.3.1. Treatment Related AE

Treatment-related AE/SAE is defined as an AE that started or worsened in severity on or after the date the study drug was first administered. TEAE information will be collected from the time of the subject's first receipt of Dostarlimab (TSR-042) monotherapy or Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination until 30 days after the last dose of Dostarlimab (TSR-042) monotherapy or Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination.

11.3.2. SAE

SAE information will be collected from the date of first dose of study drug(s) until 30 days after the last dose of Dostarlimab (TSR-042) monotherapy or Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination. If, at any time after the subject has completed participation in the study, the Investigator or study staff becomes aware of an SAE that they believe is possibly related or related to Dostarlimab (TSR-042) monotherapy or Dostarlimab (TSR-042)/Cobolimab (TSR-022) combination, then the event and any known details must be reported promptly to the Sponsor (UPMC) or its designee. The reporting instructions described in **Section 11.5.1** must be followed.

11.4. Recording AE and SAE

All AEs and SAEs experienced by a subject will be recorded on the appropriate eCRF. Information including a concise description of the event; date and time of event onset and resolution; determination of seriousness, severity, corrective treatment, outcome, relationship to study drug; and action taken regarding the study drug will be recorded.

Vital signs, laboratory results, and other safety assessments noted in **Section 10.4** will be recorded as AEs if they are determined to be clinically significant findings in the opinion of the treating Investigator. When possible, a diagnosis should be recorded as an AE, rather than symptoms or isolated laboratory abnormalities related to that diagnosis. However, when flu-like or cytokine release-like symptoms are reported, each individual symptom should be recorded as a separate AE. A medical or surgical procedure is not an AE; rather the condition leading to the procedure should be recorded as the AE. If the condition is not known, the procedure must be recorded as an AE instead. Similarly, death is not an AE, but is rather the outcome of the AE(s) that resulted in death. If the AE(s) leading to death are not known, then death must be reported as an AE.

All SAEs experienced by the subject will be entered into the CTMA and reported to the Sponsor or designee, in accordance with **Section 11.5.1**

11.5. Reporting SAE, SUAE, AESI, Special Situations and Pregnancy

11.5.1. SAE and SUAE reporting

All events meeting the definition of a serious adverse event, which occur after the date of first dose of study drug(s) and within 30 days after last dose of study drug(s), should be reported according to the CRS SAE checklist and SAE form. The initial SAE form should be sent to the following within 1 business day of the Principal Investigator becoming aware:

- Diwakar Davar, MD: davard@upmc.edu
- crssafetysubmissions@upmc.edu
- Local Institutional Review Board when reporting requirements are met

- GlaxoSmithKline: OAX37649@gsk.com or fax +44(0) 208754 7822

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within Sections B and C of the CRS SAE form:

- CTCAE term(s) and grade(s)
- Causality
- Current status of study drug
- Intervention(s) to address the AE (testing and result, treatment and response)
- Hospitalization and/or discharge dates
- Event relationship to study drug combination

Instructions for Follow-up Reports can be found in Section 11.7.

11.5.2. Reporting special situations

Special situations in this study include **Abuse**, **Misuse**, **Medication Errors**, **Overdose,** and **Accidental** or **Occupational Exposure**.

Abuse: is the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects.

Misuse: medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.

Medication error: is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

Overdose: is a deliberate or accidental administration of study treatment to a study patient, at a dose greater than that which was assigned to that patient per the study protocol and under the direction of the Investigator. If an overdose with a GSK product, the Sponsor Institution and GSK should be notified immediately, and the patient should be observed closely for AEs. Associated AEs should be treated and monitored by the Investigator. The dosage of study drug administered, any associated AEs, and/or treatment provided to the patient because of the overdose, should be reported.

Accidental /Occupational exposure: is the unintentional exposure to a study treatment as a result of one's professional or non-professional occupation, or accidental exposure to a non-professional to whom exposure was not intended (i.e., study product given to wrong patient).

Reporting Special Situations: All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure associated with a GSK product must be reported on an SAE report form to the Sponsor Institution and to GSK within 5 business days of awareness regardless

of whether or not an AE or SAE has occurred. If the abuse, misuse, medication error, overdose, or accidental / occupational exposure is associated with an AE, the SAE Report Form must be submitted to the Sponsor Institution and to GSK within 24 hours of awareness.

11.5.3. Pregnancy reporting

If the Investigator learns of a report of pregnancy at any time after signing the ICF through 150 days after last dose of therapy, the Investigator must complete a Pregnancy Form and report the pregnancy to Principal Investigator within 24 hours (following the same reporting process outlined in **Section 11.5.1**).

The Investigator will inform the subject that the Sponsor or its designee is required to gather information regarding the course and outcome of a pregnancy that has occurred after exposure to a study drug. The progress of the pregnancy must be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested.

The Investigator will be asked to obtain follow-up information no later than 2 months after the gestational period to obtain maternal/fetal/neonatal outcome and any other relevant information.

Follow-up information may be requested at additional time points. All study-related contacts involving a known pregnancy should include pregnancy status assessment until pregnancy outcome is known.

Please note that pregnancy in and of itself is not an AE or an SAE. Pregnancy should not be entered into the eCRF as an AE unless the Investigator suspects an interaction between the study drug and the contraceptive method. Additionally, all information received will be assessed for any AEs and SAEs and processed per study guidelines. If the subject is discontinued because of pregnancy, pregnancy will be documented as the reason for study discontinuation. Spontaneous abortions and stillbirths will be reported as SAEs.

11.6. Reporting to IRB and Regulatory Authorities

The Sponsor (UPMC) must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under **Section 11.6.1** to **Section 11.6.3** below. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

11.6.1. Serious and unexpected adverse reaction (SUAR)

The Sponsor (UPMC) must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);

- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);

An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

11.6.2. Findings from other studies

The Sponsor (UPMC) must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

11.6.3. Findings from animal or *in vitro* studies

The Sponsor (UPMC) must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

11.6.4. Increase rate of occurrence of serious suspected adverse reactions

The Sponsor (UPMC) must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

11.6.5. Submission of IND safety reports

The Sponsor (UPMC) must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). The Sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a FDA Form 3500A. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the Sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

11.6.5.1. Unexpected fatal or life-threatening suspected adverse reaction reports

The Sponsor (UPMC) must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the Sponsor's initial receipt of the information.

11.6.5.2. Reporting format and frequency

The FDA may require a Sponsor (UPMC) to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The Sponsor (UPMC) may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the FDA review division that has responsibility for review of the IND.

11.7. Follow Up of AE and SAE

All AEs and SAEs documented at a previous visit that are designated as either recovering/resolving or not recovered/resolved, will be reviewed by the Investigator at subsequent visits.

All AEs will be followed until resolution of AE, completion of the subject's participation, or study termination, whichever occurs first.

Serious AEs and AEs resulting in discontinuation will be followed until one of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to a baseline value, if a baseline value is available.
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct.
- The Investigator agrees that follow-up is no longer necessary.

Follow-up reports from the Investigator must be provided as indicated using the CRS SAE form within 24 hours of the Investigator's first knowledge of the new information. Additional information (i.e., hospital records, laboratory, or other diagnostic test results) should be provided if requested and/or indicated.

Rules for AE/SAE follow up apply to all subjects, including those who withdraw consent prior to study completion (to the extent allowed). The Investigator will ensure that follow up includes further investigations to elucidate the nature and/or causality of the AE/SAE. These investigations must be consistent with appropriate medical management and subject consent.

If the Investigator or designee learns of any SAE at any time after a subject has been discharged from the study and the event is considered as reasonably related to the study drug, the Investigator will report the SAE in accordance with **Section 11.5.1**.

12. Statistical Considerations

12.1. Study Design

This is a randomized phase II study of neoadjuvant dostarlimab vs. dostarlimab and cobolimab in clinical stage III/IVA resectable melanoma (AJCC stage IIIB-D, M1a). The primary objective is to evaluate the MPR rate in each arm. Secondary objectives include to evaluate radiographic response rate, relapse-free survival (RFS), overall survival, 1-year/2-year/5-year RFS rates, safety of neoadjuvant and adjuvant treatment, and rate of non-operability after neoadjuvant treatment in each arm.

The randomization of subjects to one of the two treatment arms will be in a 1:1 ratio. The UPCI Biostatistics Facility has a randomizer, an intranet application for randomly assigning patients to different treatments, which will be used for the randomization in this trial.

12.2. Study Endpoints

Primary endpoint of the study is MPR rate in either arm. Pathologic response will be assessed using previously validated criteria. Radiographic response rate will be assessed using RECIST. RFS is defined as time from randomization to relapse or death (whichever occurs first). Cases who have not had an event will be censored at the date of last disease assessment documenting the patient was free of relapse. Overall Survival (OS) is defined as the time from randomization to death from any cause. Patients who have not died will be censored at the date last known to be alive. Toxicity will be defined using the CTCAE**.**

12.3. Study Populations

Efficacy Analysis Set: includes all enrolled and randomized patients who undergo surgery. Subjects will be analyzed according to their randomized treatment group assignment.

Safety Analysis Set: includes all enrolled patients who received at least one dose of any study treatment. The safety analysis will be performed according to the actual treatment received.

12.4. Sample Size Considerations

Patients will be randomized 1:1 to either **Arm A** (neoadjuvant dostarlimab) or **Arm B** (neoadjuvant dostarlimab and cobolimab). The primary endpoint will be the MPR rate in each arm. Assuming 10% dropout rate, we will enroll 31 patients (for at least 28 evaluable patients) in each arm. 62 patients will be accrued. The MPR rate with anti-PD-1 +/- anti-CTLA-4 in high-risk operable melanoma ranges from 28% (nivolumab or pembrolizumab) to 59% (ipilimumab/nivolumab).

The sample size of 31 patients in **Arm B** (for at least 28 evaluable patients) provides 85% power at a one-sided alpha of 0.1 to detect an increase in the MPR rate from historical 28% to the target of 50% in each arm based on a one-sided z-test for one-sample proportions. If pCR rates between the two arms are different by at least 28% (such as 25% to 53%, 30% to 58% and 35% to 63%), there is at least 80% power to compare the pCR rates between the two arms. This is based on one-sided type I error rate of 0.1 using a one-sided Chi-square test for two-sample proportions.

12.5. Stopping Rules

The likelihood of achieving disease control with proposed neoadjuvant therapy must be carefully considered and balanced against the likelihood of delays in planned curative surgery because of either adverse events and/or progression on therapy. Delays in planned surgery secondary to toxicity and/or progression on neoadjuvant therapy have been observed in published neoadjuvant studies of immunotherapy in melanoma (Amaria et al., 2018; Rozeman et al., 2017; Blank et al., 2018).

The window of neoadjuvant therapy on this study (6 weeks) was carefully selected to maximize likelihood that patients would be able to receive planned surgery. However, to monitor this, the frequency of patients in whom surgery is delayed because of adverse events or progression on therapy will be monitored as a secondary endpoint.

Should the incidence of delayed surgery (defined as surgery occurring after >6 weeks from completion of therapy for reasons related to toxicity and/or progression) exceed 30% in either arm, patient enrollment will cease.

12.6. Analysis of Primary, Secondary, and Exploratory Endpoints

MPR rate will be estimated in each arm by the proportion of patients with a major pathologic response defined in Section 7.1, with corresponding exact 95% confidence intervals being reported.

Kaplan-Meier estimates of RFS and OS will be provided. The corresponding median survival time (with 95% confidence intervals) will be calculated, along with survival estimates at selected time points (e.g. 6 months, 1 years, and 2 years). Survival will be compared between the two arms with the one-sided log-rank test. The effect of treatment and other variables (e.g., baseline characteristics, biomarkers etc) on survival will be explored with Cox regression models.

Based on NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0), the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. The number of patients experiencing adverse events over their course of treatment will be characterized by type of adverse event and grade, by the time of onset in relation to the first day of therapy, and whether the event is clinically significant. The percentage of patients experiencing the grade 3 immunological toxicity will also be estimated along with its 95% confidence interval. The previously reported data do not suggest that the combination produces significantly greater toxicity profile than PD-1 monotherapy. As such, we have not incorporated an early stopping rule for toxicity into this study, but we will closely monitor toxicities, as detailed in the following Section 12.7 (“data and safety monitoring plan”).

12.7. Data and Safety Monitoring Plan

Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet monthly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- serious adverse events
- subject safety issues

- recruitment issues
- accrual
- protocol deviations
- unanticipated problems
- breaches of confidentiality

Minutes from the disease center DSMB meetings are available to those who are unable to attend in person.

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 5.0. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPCI DSMC which also meets monthly following a designated format.

Results of DSMB and/or DSMC discussions specific to this trial will be sent to GSK as well.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed twice a year rather than monthly by the disease center DSMB.

Both the UPCI DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a double locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

UPCI study staff will not physically monitor or audit other sites. Each site is responsible for conduct of the trial at their respective site per local IRB guidelines. Overall study progress will be tracked through regular email and teleconference calls between UPCI and external sites with the protocol open to enrollment.

The PI and UPCI study staff are available via email and/or telephone should any questions arise during the conduct of the study. Communication between sites will be ongoing throughout the course of this study to discuss matters of enrollment, patient status, toxicities, trial logistics and any other issues that may arise. The PI will monitor accrual and stop the study when the requirements of the study design have been fulfilled. Frequent email/telephone communication

among the group will be ongoing to address issues and confirm decisions that are made and the resolution of any questions.

UPMC CC Coordinating Center (Clinical Research Services) will maintain documentation of Serious Adverse Events (SAE) reports submitted by Participating Institutions. UPMC CC PI will review for reportability to the University of Pittsburgh IRB and communicate to participating investigators if applicable.

All SAEs will be reviewed by the disease center DSMB as well as the UPCI DSMC on a regular basis. Events will be reported to the IRB per standard external adverse event reporting guidelines.

Any new information related to the safety of the trial will be disseminated to external sites by the coordinating center staff.

13. Appendices

Appendix A: Dietary History Questionnaire for Neoadjuvant Melanoma Study (Neo-MEL-T)

Dietary history questionnaire will be administered either on paper or electronically and data entered and stored securely electronically. Instrument will be administered by PI or designee.

Detailed information for study staff:

1. Please obtain patient's username and password from study PI.
2. Please provide instructions (see below) to patients.
3. Patients are to be instructed to provide detailed dietary information either during visit (preferred) or at home.
4. Please instruct the patients to report intake as averaged over the preceding 4 weeks.

Detailed information for patients:

- Thank you for participating in this study. We are interested in evaluating your dietary history. To do this we are using a validated questionnaire termed the "Diet History Questionnaire (DHQ-3)".
- This questionnaire takes approximately 30 minutes to complete. You can do this either while receiving your therapy or at home.
- After completing the questionnaire, you will receive a Respondent Nutrition Report. This report shows estimated daily nutrient and food group intakes based on questionnaire responses. Recommended values are only available for some nutrients and food groups.
- Please feel free to discuss this with your study doctor.

Dietary study login URL:

Your username (case sensitive): _____

Your study password (case sensitive): _____

Appendix B: Pathology Specimen Processing for Neoadjuvant Melanoma Study (Neo-Mel-T)

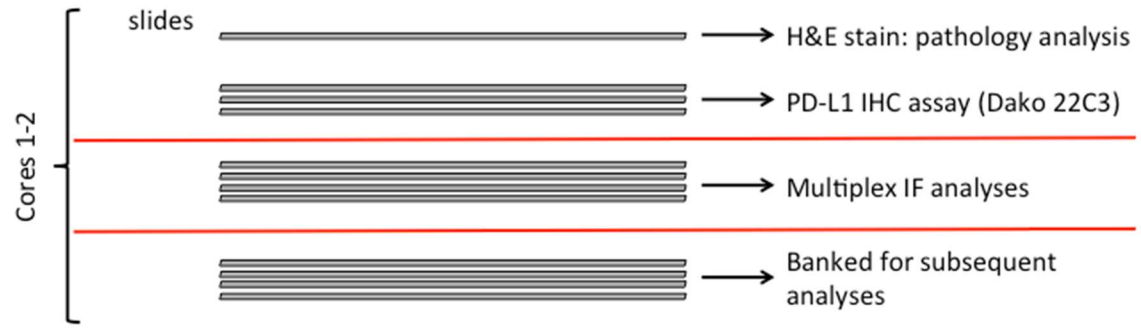
1. Pre-treatment Biopsy
    a. Definition of an adequate specimen
        i. Core or punch biopsies are permitted.
        ii. Core biopsies (preferred): preferably 6 cores using **an 16-gauge needle.**
        iii. Punch biopsies (of accessible tumor): at least 8mm punch biopsy tool. If these are obtained, they will need to be divided into 6 samples (smallest exceeding 0.5cm in breadth)
    b. Note
        i. All RNA-Seq specimens are recommended to contain ≥ 50% tumor content for optimal results. Samples submitted with less tumor content may result in data with lower precision and impact the overall value of the data. Ensure tumor cell criteria content from the pathology report is accessible to the responsible shipper for inclusion on the laboratory requisition form.
        ii. All protocol specified tissue specimens, H&E-stained slides, FFPE blocks and fresh frozen tissue samples should be submitted to the **Neo-Mel Biorepository and Pathology Core (NBPC) at Hillman Cancer Center** immediately and processing (by overnight shipping). All processed samples should be shipped no later than 5 days after processing.
        iii. If a clinical diagnosis specimen is required at your institution, the first 2 FFPE cores (Cores 1 and 2) will be prioritized for this purpose. Resulting H&E-stained slide(s) and FFPE block(s) should be submitted to **NBPC**. If institutional policy does not allow the release of FFPE block and H&E stained slides used for clinical diagnosis, please ensure (minimally) 10 and up to 15 unstained, four-micron sections are sent (sections need to be cut with clean blades and processed using RNAse free reagents).
        iv. Submit any resulting pathology reports (copies) with the samples. Please ensure pathology reports do not contain any patient identifiers when shipped.
        v. Histology diagnoses should be performed according to the WHO 2015 classification.
    c. Precautions
        i. Prior to the scheduled sample collection, the institutional study coordinator will alert the study pathologist to the date and time of tissue procurement.
    d. Biopsy procedure
        i. Ensure Pathologist training has been documented for the reporting Pathologist per institution's delegation of responsibilities log (PI and study coordinator manage this document).
        ii. To ensure a quality tissue sample for core biopsies, a rapid on site evaluation (ROSE) methodology is highly recommended to evaluate the adequacy of the sample.
            1. Two procedures are suggested: fine needle aspiration (FNA) smears, or touch prep of tissue cores followed by cytology evaluations. ROSE cytology slides will stay in the participant institution.

2. A minimum of 3 and up to 5 tissue cores should be collected, including 2 for FFPE processing and 3 fresh frozen cores. These cores will be processed as depicted in **Figure 1** (**Proposed Biomarker Analyses for 1st FFPE Biopsy Sample & Priority of Analyses**).

e. Biopsy allocation
   i. Cores 1and 2:
      1. Immediate and overnight fixation in 10% buffered formalin for paraffin embedding, usually within 20-24 hour after fixation. For biopsies performed on Friday, fixation time may extend to 48-72 hours.
      2. FFPE Processing: The cores in fixation will be processed at the local site.
      3. Each tissue core should be placed in a separate block. H&E-stained slide(s) and FFPE block(s).
   ii. Cores 3-5 (ex-UPMC):
      1. Flash frozen in liquid nitrogen.
      2. Each tissue core should be placed in separated labeled cryovials.
   iii. Cores 3-5 (at UPMC):
      1. Core 3-5: scRNA sequencing and single cell suspension.

f. Send all cores to **Neo-Mel Biorepository and Pathology Core (NBPC) at Hillman Cancer Center.**

Figure 1: Proposed Biomarker Analyses for 1st (pre-treatment) Biopsy Sample & Priority of Analyses



Notes:
#scRNA seq (single-cell sequencing)
$TIL analyses

2. Surgical Resection Specimen
   a. Definition of an adequate specimen

i. Adequacy of surgical specimen is defined in **Sections 6.12.1 to 6.12.5** of the clinical trial protocol.

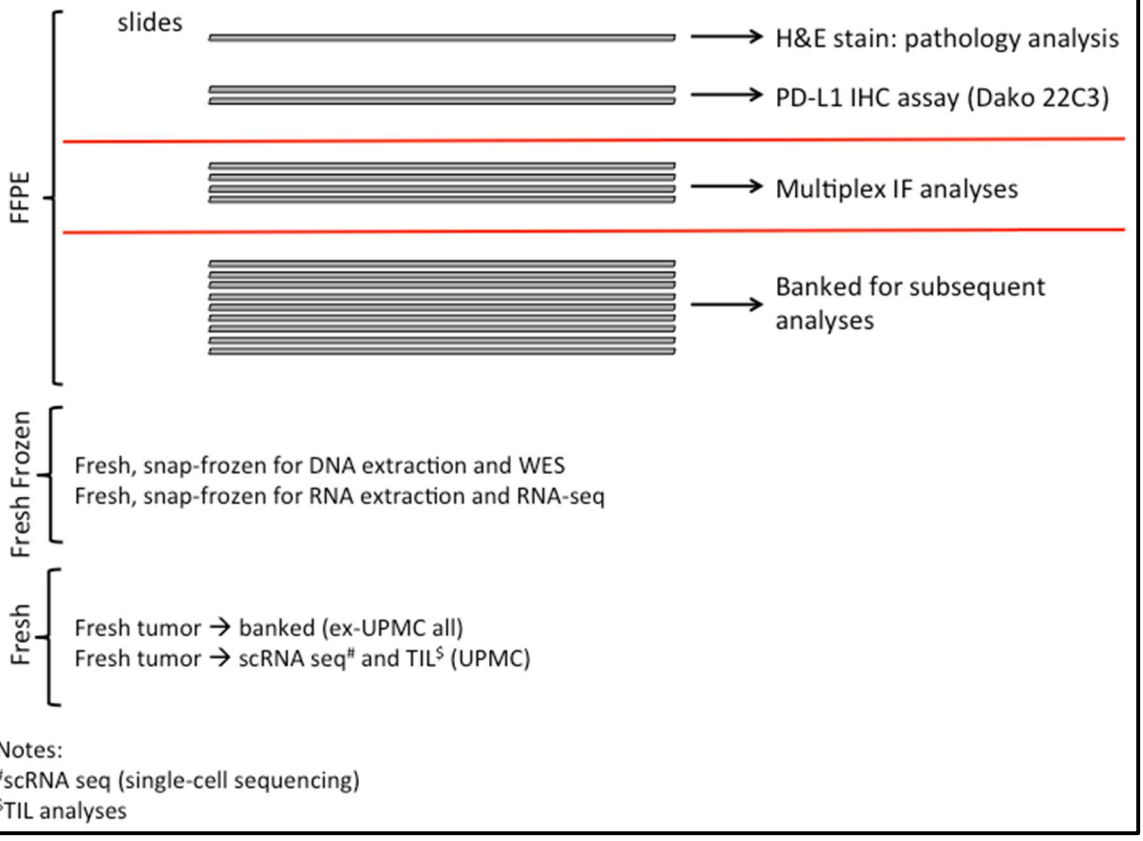
b. Note
   i. Prior to the scheduled sample collection, the institutional study coordinator will alert the local study pathologist to the date and time of tissue procurement.
   ii. Resection specimens will be brought immediately to a tissue processing laboratory in the institutional department or service of pathology where the study pathologist or designate (e.g. existing Institutional tumor bank pathologist assistant personnel) will serially section the tumor to harvest samples for study.
   iii. Harvest of research samples should happen **within 30 minutes of tissue resection** from the patient.
   iv. Sample collection should be conducted in a manner that does not compromise routine pathology diagnosis and case reporting.

c. Precautions
   i. Prior to the scheduled sample collection, the institutional study coordinator will alert the study pathologist to the date and time of tissue procurement.

d. Definitive resection sample dissection and allocation
   i. Resection specimens need to be examined for diagnostic purposes as depicted in **Figure 2** (**Proposed Priority of Biomarker Analysis for 2nd Surgical Sample & Priority of Analyses**) gross tumor size, margin and invasion assessments.
   ii. Tumor needs to be measured in all dimensions in centimeters.

iii. By gross examination select a non-necrotic, "viable", tumor area to collect a minimum fresh specimen for flash freezing in liquid nitrogen (**Figure 2**). If possible, an 8x8x8 mm specimen should be collected.

Figure 2: Proposed Biomarker Analyses for 2nd (on-treatment) Surgical Sample & Priority of Analyses



iv. In cases where the tumor "viable" areas cannot be grossly determined, a frozen section examination of the tissue is recommended. In these cases, an OCT-embedded fresh-frozen tissue specimen should be prepared. If no malignant cells are detected, two more attempts of examining tumor area content by frozen H&E section should be conducted. If no malignant cells are detected in the second attempt, both fresh frozen tumor samples should be submitted (*sections need to be cut with clean blades and processed using RNAse free reagents*).

v. H&E-stained slide(s) from frozen section(s), fresh frozen tissue and FFPE samples should be submitted to **UPCI Melanoma Program (attention: Neo-Mel-T Study)** after processing for slide scanning and quality control purposes.

1. Note: The first two sets of 10 cases collected in the trial will be evaluated by the **UPCI Melanoma Program (attention: Neo-Mel-T Study)** to assess best practices for fresh sample collection. Cases will be evaluated for quality, and sites may receive feedback.

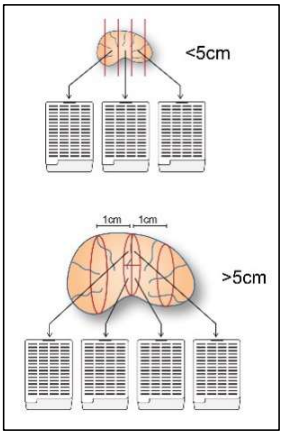
Appendix C: Case Report Form for Pathologic Response Assessment

In this study, pathologic response will be assessed as follows:

- LN/tumor resection specimens will be processed at the local institution following CAP and CLIA guidelines.
- Immediate sampling of the tumor and overnight fixation in 10% buffered formalin for paraffin embedding, usually within 20-24 hour after fixation. For biopsies performed on Friday, the fixation time may extend to 48-72 hours.
- For histopathological evaluation, samples will be processed as outlined in **Section 7.1** of the clinical trial protocol and as depicted in **Figure 3 (Methods of Assessing %RVT In Patients Receiving Neoadjuvant Therapy**).

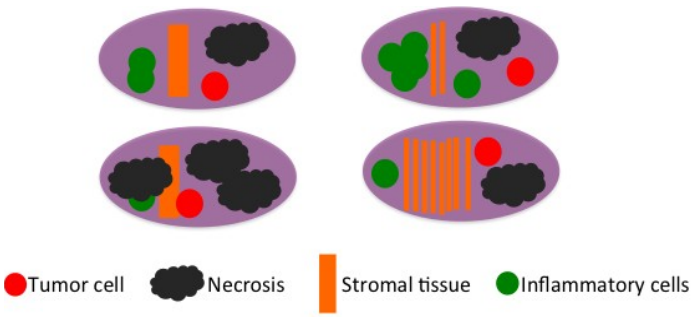
Figure 3: Methods of Assessing %RVT In Patients Receiving Neoadjuvant Therapy

Step 1:
Serial sections depending on size of tumor/LN:
- Largest grossly positive lymph node/tumor measures ≤5 cm
- Largest grossly positive lymph node/tumor measures >5 cm



Step 2:
Assessment:
- ≤5 cm: submit entire LN/tumor at 2mm serial sections
- **>5 cm: submit representative sections**
  - **Complete sections from LN/tumor <5cm**
  Representative sections from LN/tumor >5cm

Step 3:
1. **Calculate residual viable tumor (RVT) = total surface area of RVT**
2. **Calculate total tumor bed area = total area of regression + RVT + necrosis**



Step 4:
- **%irRVT = total RVT/total tumor bed area x 100**
- **Each surgical sample will be scored by the initial reading pathologist and independently by 3 blinded pathologists**
- **Final irRVT is the mean score of 3 independent reads**
- **%irRVT for each sample will be reported as mean +/-SD**

Adapted from Tetzlaff et al (Ann Oncol 2018), Cottrell et al (Ann Oncol 2018)

- A **standardized reporting form (Appendix C: Case Report Form for Pathologic Response Assessment)** will be provided to pathologists to assess diagnosis, pathological features and MPR.
    - Sections reveal completely regressed/partially viable/mostly viable melanoma involving __ of __ lymph nodes or fibroconnective tissue.
    - Overall tumor response (pathologist to indicate)
        - Complete pathologic response (0% RVT)
            - Yes
            - No
        - Major pathologic response (≤10% RVT)
            - Yes
            - No
        - Pathologic partial response (<10 to ≤50% RVT)
            - Yes
            - No
        - Pathologic non-response (>50% RVT)
            - Yes
            - No
    - An evaluation of the completely treated tumor bed reveals:
        - Viable tumor: Present/Not identified
            - Extent: __%
        - Tumoral melanosis: Present/Not identified
            - Extent: __%
        - Tumoral necrosis: Present/Not identified
            - Extent: __%
        - Fibrosis: Present/Identified
            - Extent: __% of the tumor bed occupied by fibrosis
            - Hyalinized: __%
            - Proliferative: __%
        - Inflammatory infiltrate: Present/Not identified
            - Extent: __% and Composition

In order to achieve accurate and reproducible pathologic assessment in neoadjuvant treated specimens, the following requirements for the gross assessment and submission of tissue following neoadjuvant treatment as recommended by the International Neoadjuvant Melanoma Consortium (see figure below):

- If the largest grossly positive lymph node measures ≤ 5 cm in greatest dimension, then the entire lymph node should be entirely submitted at 2 mm serially sectioned intervals.
- For any grossly positive lymph node measuring > 5 cm in greatest dimension, then representative sections of the largest lymph nodes may be utilized to avoid oversampling as indicated below.
    - Following serial sectioning of each lymph node, for those grossly positive nodes > 5 cm, sections representing a complete cross section of

the entire surface area should be submitted per 1 cm of each grossly positive lymph node.
    - All lymph nodes < 5cm in specimens where the largest node(s) exceeds 5 cm should be submitted entirely.
- The local institutional study pathologist will assess each case for Major Pathological Response (MPR) as outlined in **Section 7.1** of the clinical trial protocol and results will be documented in the clinical trial database.
- MPR should be reported as average percentage of each tumor slide examined. It is recommended to circle tumor area and malignant cell areas and determine the tumor cell content on each slide, and then calculate the average malignant cell content of the entire case.
- Upon completion of the MPR assessment, one representative FFPE tumor block and all diagnostic H&E-stained slides including tumor, normal and lymph nodes will be submitted to **UPCI Melanoma Program (attention: Neo-Mel-T Study Pathology Substudy)** for review, scanning/ storage and analysis in an **Aperio digital pathology system**.
- All slides will be returned to the submitting institution in 72 hours. Alternatively, H&E-stained recuts would be also accepted.
    - The pathology report (de-identified copy) issued at the participating institution should be submitted along with the FFPE H&E-stained slide(s) and block(s) to the **UPCI Melanoma Program (attention: Neo-Mel-T Study Pathology Substudy)**. Histology diagnoses should be performed according the WHO 2015 classification.

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