A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an anti-PD-1 Monoclonal Antibody, in Patients with Advanced Solid Tumors

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Clinical Research Organization:	Pharmaceutical Research Associates, Inc. 4130 Parklake Avenue, Suite 400 Raleigh, NC 27612 USA	
Protocol Number:	4010-01-001	
IND Number:	126472	
EudraCT Number:	2016-000320-26	
Study Drug Name:	Dostarlimab (TSR-042)	
Development Phase:	1	
Date of Original Protocol:	03 December 2015	
Date of Amendment 1:	26 January 2016	
Date of Amendment 2:	31 October 2016	
Date of Amendment 3:	09 October 2017	
Date of Amendment 4:	03 July 2018	
Date of Amendment 5:	10 May 2019	
Version of Protocol:	6.0 (10 May 2019)	

The study will be conducted according to the protocol and in compliance with Good Clinical Practice, with the Declaration of Helsinki, and with other applicable regulatory requirements.

[redacted]

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title (Study Number): **A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an anti-PD-1 Monoclonal Antibody, in Patients with Advanced Solid Tumors (4010-01-001)**

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.

[redacted]

INVESTIGATOR SIGNATURE PAGE

Declaration of the Principal Investigator

Title (Study Number): **A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an anti-PD-1 Monoclonal Antibody, in Patients with Advanced Solid Tumors (4010-01-001)**

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/Institutional Review Board, in accordance with the study protocol, the current International Council on Harmonisation Guideline for Good Clinical Practice, 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.

Principal Investigator

<<Add **PI Name, Degree(s)**	**Date**
<<Add **PI Title**	
<<Add **Institution Name**	

SYNOPSIS

Name of Sponsor/Company: TESARO, Inc.	
Name of Investigational Product: Dostarlimab (TSR-042)	
Name of Active Ingredient: TSR-042	
Title of Study: A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an anti-PD-1 Monoclonal Antibody, in Patients with Advanced Solid Tumors	
Study Center(s): Up to 3 sites in Part 1 and approximately 150 sites in Part 2	
Studied Period (years): Estimated date first patient enrolled: March 2016 Estimated date last patient completed: February 2020	**Phase of Development:** Phase 1

Objectives:

Primary Objectives:

Part 1 – Dose Escalation Cohorts:

- To evaluate the safety and tolerability of dostarlimab in patients with advanced solid tumors and determine the recommended Phase 2 dose (RP2D) and schedule

Part 2A – Fixed-Dose Safety Evaluation Cohorts:

- To evaluate the safety and tolerability of dostarlimab at fixed-dose in patients with advanced solid tumors and determine the RP2D and schedule

Part 2B – Expansion Cohorts:

- Cohorts A1 [redacted]: To evaluate the antitumor activity of dostarlimab in patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) cancers, including dMMR/MSI-H endometrial cancer (EC) (Cohort A1), non-endometrial dMMR/MSI-H cancers (Cohort F), in terms of objective response rate (ORR) and duration of response (DOR) by independent blinded central review using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- [redacted]

Secondary Objectives:

Part 1 – Dose Escalation Cohorts:

- To evaluate irORR as assessed by the Investigators using irRECIST

Part 1 and Part 2:

- To characterize the pharmacokinetic (PK) profile of dostarlimab
- To evaluate the immunogenicity of dostarlimab
- To evaluate additional measures of clinical benefit, including:

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- Immune-related disease control rate (irDCR) based on Investigators' assessment using irRECIST
- Immune-related duration of response (irDOR) based on Investigators' assessment using irRECIST
- Immune-related progression-free survival (irPFS) based on Investigators' assessment using irRECIST
- Progression-free survival (PFS) based on independent blinded central review using RECIST v1.1 (Cohorts A1, [redacted])
- Immune-related overall response rate (irORR) based on Investigators' assessment using irRECIST (Cohorts A1, [redacted])
- ORR based on independent blinded central review using RECISTv1.1 in dMMR/MSI-H and Polymerase ε-mutated (POLE-mut) cancers (Cohorts A1 and F combined)
- DOR based on independent blinded central review using RECISTv1.1 in dMMR/MSI-H and POLE-mut cancers
- Disease control rate (DCR) based on Investigators' assessment using RECIST v1.1 (Cohorts A1, [redacted])
- Overall survival (OS)

Exploratory Objectives:

- To characterize the pharmacodynamic (PDy) profile of dostarlimab
- To explore changes in intratumoral cells and circulating biomarkers in the blood following treatment with dostarlimab
- To explore the profile of tumor-infiltrating lymphocytes (TILs), tumor cell characteristics including genomic alterations (e.g., MMR/MSI and POLE), and/or circulating biomarkers prior to treatment with dostarlimab and correlate with clinical benefit
- Patient-reported outcomes (PROs) [European Quality of Life scale, 5-Dimensions (EQ-5D-5L) and European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30)] in patients in Cohorts A1 [redacted] enrolled under Amendment 3 or subsequent amendments

Methodology:

Overall

This is a multicenter, open-label, first-in-human Phase 1 study evaluating the anti-programmed death-1 (anti-PD-1) antibody dostarlimab in patients with advanced solid tumors who have limited available treatment options as determined by the Investigator. The study will be conducted in 2 parts.

Using a modified 3+3 design, Part 1 (dose escalation) will initially evaluate 3 ascending weight-based dose levels (DLs) of dostarlimab, 1 mg/kg, 3 mg/kg and 10 mg/kg, administered via intravenous (IV) infusion. Further dose escalation may be considered in additional cohort(s) at potential DLs of 15mg/kg and/or 20mg/kg (not to exceed 20 mg/kg) following agreement between the Investigators and Sponsor. In Part 1, at any DL where the dose-limiting toxicities (DLTs) are observed in <33% of DLT-evaluable

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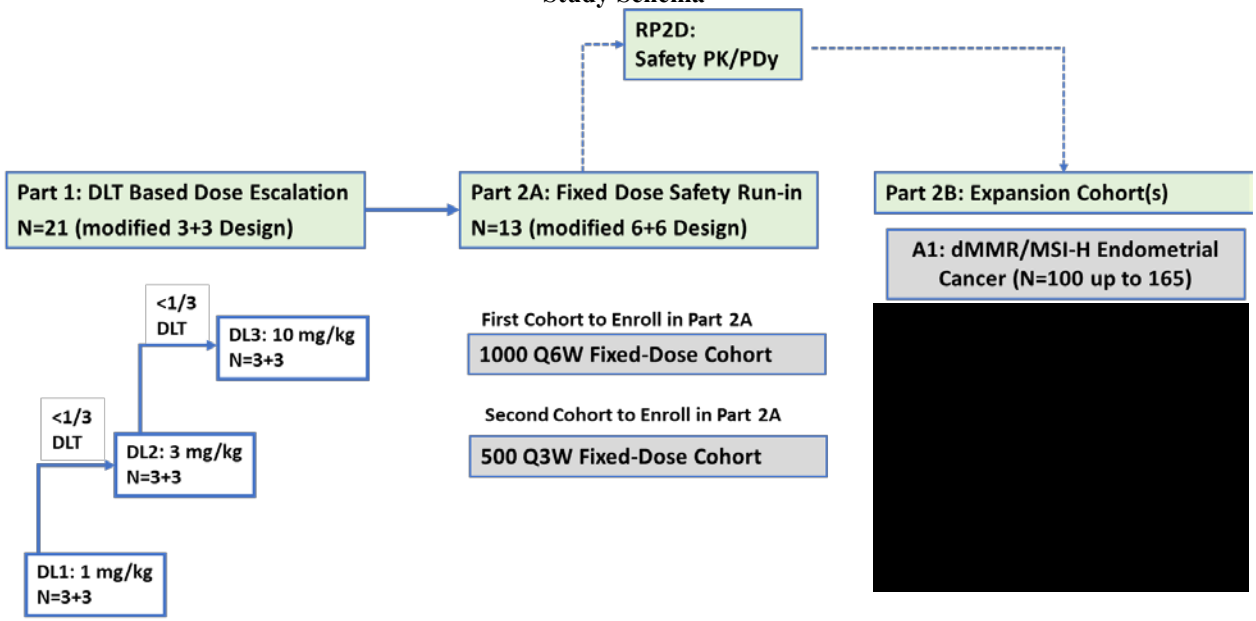
patients, up to 6 additional patients may be enrolled to obtain additional data to better characterize the PK/PDy profiles and contribute to determination of the RP2D.
Part 2 of the study will be conducted in two subparts (Part 2A and Part 2B) to explore the safety and clinical activity of dostarlimab administered as a fixed-dose (i.e., not weight-based).
In Part 2A, following the completion of Part 1, the safety and tolerability of dostarlimab will be evaluated at fixed-dose levels of 500 mg every 3 weeks (Q3W) and 1000 mg every 6 weeks (Q6W) using a modified 6+6 design. Each dose level will enroll 6 patients initially. Enrollment for Q6W cohort will begin first, followed by enrollment in the Q3W cohort. The recommended dosing and schedule in Part 2B will be determined based on PK/PDy profile and the safety and tolerability data from the dosing schedules tested in Part 1 and Part 2A.
In Part 2B, the clinical activity and safety of dostarlimab at the RP2D will be evaluated in patients with specific tumor types (Cohorts A1, A2 and E) and in non-endometrial cancer (non-EC) patients whose tumors have dMMR/MSI-H cancer or POLE-mutated (i.e. cancers harboring mismatch repair deficient [dMMR/microsatellite instability or mutations in the exonuclease domain of polymerase ε [POLE-mut]) tumors regardless of histology (Cohort F).
Cohort A1 will enroll approximately 100 with the potential for up to 165 patients with dMMR/MSI-H EC, [redacted] Adjustments to enrollment within cohorts may occur based on emerging data and Sponsor's decision.
The study will be conducted in conformance with Good Clinical Practice (GCP).

Study Schema[a]



Abbreviations: DL=dose level; DLT=dose-limiting toxicity; dMMR=mismatch repair deficient; MSI-H=microsatellite instability high; MSS=microsatellite stable; [redacted] N or n=number (of patients); MMR-proficient=mismatch repair proficient; POLE-mut= polymerase ε mutated; Q3W=every 3 weeks; Q6W=every 6 weeks; RP2D=recommended Phase 2 dose;
[a] Adjustments to enrollment within cohorts may occur based on emerging data and Sponsor's decision.

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Part 1: Dose Escalation Phase

Cohorts will be enrolled sequentially and will follow a modified 3+3 design with DL1 (1 mg/kg) being the first cohort to enroll. At DL1, 3 patients will be enrolled and if there are no DLTs (see DLT criteria below) observed in any of the 3 patients through the DLT observation period (i.e., through Cycle 1/Day 28), then the next higher DL cohort will open for enrollment. If 1 of the first 3 patients experiences a DLT, then 3 additional patients will be enrolled (total of 6 evaluable patients at the same DL).

Dose escalation will continue until the maximum tolerated dose (MTD) is reached or may be stopped at any DL up to the highest planned dose (i.e., 20 mg/kg in an additional cohort) based on emerging safety and PK/PDy data, subject to agreement between the Investigators and Sponsor. The MTD will be defined as the dose level -1 of the dose level that is found to be unsafe based on a modified 3+3 design and have confirmed DLT rate <33% from at least 6 patients during Cycle 1 of treatment.

Up to 6 additional patients may be enrolled in any DL with DLTs observed in <33% of DLT- evaluable patients to better characterize PK/PDy profile of dostarlimab. These patients will receive dostarlimab during Cycle 1 only on Day 1 (i.e., no treatment on Cycle 1/Day 15) with the subsequent doses administered on Cycle 2/Day 1 and every 2 weeks thereafter. Cycle 1/Day 1 administration will be followed by DLT observation period of 28 days for safety observations and PK/PDy blood sampling. These additional patients will not be considered evaluable for dose escalation purposes (i.e., not included into the DLT-evaluable population), but will contribute to the overall safety assessment of the DL.

DLT criteria (as assessed during Cycle 1 in Part 1 and Cycle 1 in Part 2A:

- Any treatment-related Grade ≥ 3 non-hematologic clinical (non-laboratory) toxicity excluding:
  - Nausea and vomiting resolving to ≤ Grade 1 within 48 hours
  - Grade 3 diarrhea with duration < 48 hours
  - Grade 3 fatigue with duration < 7 days
  - Infusion-related reaction ≥ Grade 3 or recurrent infusion-related reaction ≥2 despite adequate pre-medication
- Any treatment-related non-hematologic toxicity specifically defined as:
  - ≥ Grade 2 uveitis, eye pain, or blurred vision that does not resolve with topical therapy within 2 weeks
  - ≥ Grade 2 immune-related endocrine toxicity that requires hormone replacement (except Grade 2 thyroiditis or thyroid dysfunction)
  - ≥ Grade 2 colitis or diarrhea that persists for ≥ 7 days despite adequate steroid therapy
  - Any toxicity that results in a treatment delay of ≥ 7
- Any treatment-related Grade ≥ 3 non-hematologic laboratory abnormality if:
  - Medical intervention is required to treat the patient, or
  - The abnormality leads to hospitalization, or
  - The abnormality persists for ≥ 7 days
- Any treatment-related hematologic toxicity specifically defined as:

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- Grade 4 thrombocytopenia for ≥ 7 days, or Grade 3 or 4 associated with bleeding or requiring platelet transfusion
- Grade 4 neutropenia for ≥ 7 days, or Grade 3 or 4 associated with infection or febrile neutropenia
- Grade 4 anemia, or Grade 3 anemia requiring blood transfusion

Toxicities will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03. If multiple toxicities occur, the presence of DLT will be graded based on the most severe toxicity observed. Before Cycle 2/Day 1, each patient must be assessed by the Investigator as to whether the patient experienced a DLT to confirm the patient may continue treatment. Patients who experience a DLT will be permanently discontinued from treatment.

Part 2: Fixed-Dose Safety Evaluation and Expansion Phase

Part 2 of the study will be conducted in 2 subparts: Part 2A (fixed-dose safety evaluation cohort) and Part 2B (expansion cohorts).

Part 2A: Following the completion of Part 1, safety and tolerability of dostarlimab at fixed-dose levels of 500 mg Q3W and 1000 mg Q6W will be evaluated in patients with advanced solid tumor using a modified 6+6 design. Each cohort will initially enroll 6 patients and enrollment for the Q6W cohort will begin first followed by enrollment in the Q3W cohort. The cycle durations and DLT observation periods are 21 days for the Q3W cohort and 42 days for the Q6W cohort. Patients in each cohort will receive dostarlimab via IV infusion on Day 1 of every cycle.

If ≤ 1 patient experiences DLT out of 6 evaluable patients in each cohort, the respective dose will be declared safe. If ≥ 2 patients experience DLT in any cohort, then 6 additional patients will be enrolled in that particular cohort. If ≤ 3 patients out of 12 evaluable patients in the cohort experience DLT, then the respective dose will be considered safe. If ≥ 33% of evaluable patients experience DLT at any time during the DLT period in any cohort, the dose will be considered unsafe and enrollment in the cohort will stop.

The DLT criteria for Part 1 will be applied to Part 2A. The DLT period in Part 2A will be assessed through Day 21 and Day 42 in the Q3W and Q6W fixed-dose cohorts, respectively.

Part 2B: Part 2B of the study will enroll patients in up to 4 expansion cohorts. Cohorts A1, A2, E and F will enroll patients with the following tumor types: endometrial cancer in separate cohorts consisting of dMMR/MSI-H tumors (Cohort A1) and MMR-proficient/MSS tumors [redacted]

Patients in Part 2B will be treated with the RP2D determined based on data from Part 1 and Part 2A. As of February 2017, Part 1 and Part 2A have been completed. Both fixed doses tested in Part 2A were found to be safe, and the RP2D was determined to be 500 mg dostarlimab Q3W for the first 4 cycles, followed by 1000 mg dostarlimab Q6W for all subsequent cycles. This dosing schedule will be used in Part 2B.

General Study Conduct

Patients in Part 1 being evaluated for DLT-based dose escalation will be treated with dostarlimab on Cycle 1/Day 1 and Cycle 1/Day 15 and will be followed by on-treatment visits throughout the first 28 days for safety assessments and blood sampling for PK/PDy. dostarlimab will be administered on Day 1 and Day 15 in all subsequent cycles in Part 1. Patients enrolled specifically for additional PK/PDy sampling will not receive dostarlimab on Cycle 1/Day 15, but will subsequently follow an every 2 week (Q2W) schedule throughout the rest of the study treatment period.

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All patients in Part 2A will receive either 500 mg Q3W or 1000 mg Q6W of dostarlimab on Day 1 of every cycle (note that Q6W and Q3W dosing comprise 42- and 21-day cycles, respectively). In Part 2B, patients will be treated with the RP2D determined based on data from Part 1 and Part 2A. Blood samples for determination of serum levels of dostarlimab and anti-dostarlimab antibodies will be collected from patients in both Part 1 and Part 2. In addition, blood samples obtained in Part 1 and Part 2 of the study will be assessed for PD-1 receptor occupancy. In patients who consent to optional serial biopsies, these biopsies will be obtained prior to initiation of treatment, approximately 4-6 weeks after receiving the first dostarlimab dose, and whenever possible, at the time of progressive disease (PD). If a patient has had a biopsy prior to screening and within 12 weeks of study treatment, that biopsy may be accepted as the screening biopsy. Safety assessments conducted throughout the treatment period include symptom-directed physical examinations, vital signs, electrocardiograms (ECGs), Eastern Cooperative Oncology Group (ECOG) performance status, and clinical laboratory assessments, including complete blood count (CBC) with differential (including absolute lymphocyte count [ALC] and absolute neutrophil count [ANC]), coagulation profile, chemistry, thyroid panel, urinalysis, and pregnancy testing. In Part 1, radiographic evaluations (computed tomography [CT]/magnetic resonance imaging [MRI] of chest, abdomen, and pelvis) and appropriate testing of serum-based tumor markers, where applicable (e.g., CA-125 for ovarian cancer [OC] patients), to assess extent of disease will be conducted every 10 weeks (±10 days). After 1 year of radiographic assessments, patients will have imaging performed every 12 weeks (84 ±10 days). In Part 2A and Part 2B, radiographic evaluations and appropriate testing of serum-based tumor markers, where applicable (e.g., CA-125 for OC patients), to assess extent of disease will be conducted 12 weeks after receiving the first dostarlimab dose and every 6 weeks thereafter (±10 days), and as clinically indicated while on study treatment independent of cycle delays and/or dose interruptions, and/or at any time when progression of disease is suspected. Brain scans will be conducted if clinically indicated. Bone scans will be conducted per standard of care. In Part 2A and Part 2B, patients who remain on treatment after 1 year will have imaging performed every 12 weeks (84 ±10 days). If a patient discontinues treatment for a reason other than progression, death, withdrawal of consent, or loss to follow-up, radiographic scans and appropriate testing of serum tumor markers should continue at the specified intervals. In Part 2B, all radiographic images/scans will be sent to a central imaging vendor upon acquisition and archived for potential future evaluation. Per irRECIST, complete response (CR) or partial response (PR) should be confirmed; tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (i.e., approximately 6 weeks after the previous scan), whichever is clinically appropriate. It is highly recommended that confirmation of PD occurs within 4 to 6 weeks of the first PD assessment; patients may remain on study treatment while awaiting confirmation provided the patient is clinically stable. Following confirmation of PD, if the Investigator believes there is clinical benefit, clinically stable patients without major safety issues may remain on treatment following discussion with the Medical Monitor. All patients will undergo an end-of-treatment (EOT) visit conducted 30 days (±7 days) for the Q2W and Q3W schedules or 42 days (±7 days) for the Q6W schedule after the last date of study drug administration. Patients will also undergo a safety follow-up visit conducted 90 days (±7 days) after the last date of study drug administration. After the 90-day safety follow-up visit, patients will enter the post-treatment follow-up period for telephone assessment of survival status every 90 days (±14 days).

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Patient-reported outcomes (PRO) assessments (EQ-5D-5L and EORTC QLQ-C30) will be collected during scheduled visits for all patients in Cohorts A1 and F enrolled under Amendment 3 or subsequent amendments, i.e. every 3 weeks ±7 days for the first 12 weeks, in alignment with study drug administration, and every 6 weeks (±7 days) thereafter, in alignment with tumor imaging assessments, while the patient is receiving study treatment. Once a patient discontinues treatment, PRO assessments will be performed during the end-of-treatment (EOT) visit, the safety follow-up visit, and during the post-treatment follow-up period every 90 days (±14 days).

All adverse events (AEs) and serious adverse events (SAEs) will be collected and recorded for each patient from the day of signing the informed consent form (ICF) until 90 days after end of treatment visit or until alternate anticancer treatment has been initiated, whichever occurs earlier; any pregnancies that occur within 150 days post-treatment are to be reported. All AEs and SAEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up or withdraws consent, or until the patient has died.

MMR/MSI and POLE testing for Cohorts A1, A2, and F:

Patients can be screened based on local MMR/MSI testing results using immunohistochemistry (IHC), polymerase chain reaction (PCR), or next generation sequencing (NGS) performed in a certified local laboratory, but patient eligibility needs to be determined by MMR IHC results. For patients with available local MMR IHC results for the respective cohort(s), tumor samples have to be submitted to a central IHC laboratory and its quality has to be checked and cleared prior to C1D1. For patients without available local MMR IHC test results (patients with local PCR or NGS test results), tumor samples have to be submitted directly to central IHC laboratory and central IHC results have to confirm eligibility prior to proceeding with other screening procedures. After the central IHC test is completed, remaining tumor tissue may be sent to a central NGS laboratory for further testing.

Patients who are considered for the study based on POLE mutation must have the local results available showing tumor mutation(s) in the exonuclease domain of the POLE gene (amino acid residues 268-471) to begin screening. Patients must have the quality of submitted tumor samples checked and cleared by a central IHC laboratory prior to receiving study treatment.

Pharmacokinetics, Pharmacodynamics, and Biomarkers

Serum samples for PK determination as well as antidrug antibody (ADA) assessment will be collected prior to, during, and after dostarlimab administration. The serum samples will be analyzed using enzyme-linked immunosorbent assay (ELISA) for dostarlimab PK analysis and electrochemiluminescence (ECL) for dostarlimab ADA analysis, respectively. Area under the concentration-time curves (AUCs) will be derived based on the results of serum PK sample analysis. Results of 3-tier ADA assays (screening, confirmation and titer) and competitive ligand binding assay as neutralizing antibody assay (NAb) will be correlated with clinical activity, PK, as well as safety assessments.

During Part 1 and Part 2, blood cells may be assessed for programmed death-1 (PD-1) receptor occupancy prior to and after the first dose of dostarlimab and may be considered for selection of the RP2D.

To better understand the effect of dostarlimab on the immune response and to potentially identify markers that are predictive and/or prognostic of drug activity, blood samples for biomarker analyses, such as assessing changes in serum cytokines and gene expression will be obtained pre-dose on Day 1 of each cycle up to and including Cycle 6 in both Part 1 and Part 2.

Biomarkers may also be evaluated in archival and newly obtained tumor samples from patients where available. In the subset of patients who consent to optional serial biopsies, biomarkers will be evaluated in

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new tumor samples obtained approximately 4-6 weeks after receiving the first dostarlimab dose and, whenever possible, at the time of PD. In addition to monitoring immune responses, tumor genomic alterations (e.g., MMR/MSI and POLE) may be correlated with other immune-related biomarkers and with clinical activity in Part 2.

Number of Patients (Planned):

Part 1: A total of approximately 36 patients is expected, but this may increase to approximately 54 patients; this assumes approximately 18 to 36 patients per 3 proposed dose levels (1 mg/kg, 3 mg/kg, and 10 mg/kg) with potentially an additional 6 to 12 patients in an additional dose cohort.

Part 2: A total of up to 704 patients. Up to 24 patients may be enrolled in Part 2A; in Part 2B, Cohort A1 will be increased to enroll approximately 100 with the potential for up to 165 patients, [redacted] Adjustments to enrollment within cohorts may occur based on emerging data and Sponsor's decision.

Main Criteria for Inclusion:

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Patient is at least 18 years of age.
2. Patient has proven recurrent or advanced solid tumor and has disease progression after treatment with available anti-cancer therapies, or is intolerant to treatment that meets the requirements for the part of the study they will participate in:
   a. Part 1: Any histologically or cytologically proven recurrent or advanced solid tumor
   b. Part 2A: Any histologically or cytologically proven recurrent or advanced solid tumor
   c. Part 2B: Histologically or cytologically proven recurrent or advanced solid tumor with measurable lesion(s) per RECIST v.1.1 and meets one of the following disease types:

      The criteria below should be met for patients participating in:
      i. Cohort A1 (dMMR/MSI-H endometrial cancer) and
      ii. [redacted]

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- [redacted]

iii. Tumor MMR/MSI status: Patients can be screened based on local MMR/MSI testing results using immunohistochemistry (IHC), polymerase chain reaction (PCR), or next generation sequencing (NGS) performed in a certified local laboratory, but patient eligibility needs to be determined by MMR IHC results. For patients with available local MMR IHC results for the respective cohort(s), tumor samples have to be submitted to a central IHC laboratory and its quality has to be checked and cleared prior to C1D1. For patients without available local MMR IHC test results (patients with local PCR or NGS test results), tumor samples have to be submitted directly to central IHC laboratory and central IHC results have to confirm eligibility prior to proceeding with other screening procedures.
After the central IHC test is completed, remaining tumor tissue may be sent to a central NGS laboratory for further testing.

iv. [redacted]

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- [redacted]
  - Tumor MMR/MSI status: Patients can be screened based on local MMR/MSI testing results using immunohistochemistry (IHC), polymerase chain reaction (PCR), or next generation sequencing (NGS) performed in a certified local laboratory, but patient eligibility needs to be determined by MMR IHC results. For patients with available local MMR IHC results for the respective cohort(s), tumor samples have to be submitted to a central IHC laboratory and its quality has to be checked and cleared prior to C1D1. For patients without available local MMR IHC test results (patients with local PCR or NGS test results), tumor samples have to be submitted directly to central IHC laboratory and central IHC results have to confirm eligibility prior to proceeding with other screening procedures. After the central IHC test is completed, remaining tumor tissue may be sent to a central NGS laboratory for further testing.
  - Patients who are considered for the study based on POLE mutation must have local results available showing tumor mutation(s) in the exonuclease domain of the POLE gene (amino acid residues 268-471) to begin screening. Patients must have the quality of submitted tumor samples checked and cleared by a central IHC laboratory prior to receiving study treatment.

3. Patients participating in Part 2B must have archival tumor tissue available that is formalin-fixed and paraffin-embedded.
   - For patients who do not have archival tissue, a new biopsy must be performed to obtain a tissue sample prior to study treatment initiation. For patients without available archival tissue, biopsy should be taken from the tumor lesions (either primary or metastatic) that have easy accessibility and low biopsy-associated risks and will exclude biopsies of the liver, brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach or bowel.
4. Female patients must have a negative serum pregnancy test within 72 hours of the first dose of study medication; unless they are of non-childbearing potential. Non-childbearing potential is defined as:
   a. ≥ 45 years of age and has not had menses for > 1 year
   b. Amenorrheic for < 2 years without a hysterectomy and oophorectomy and have a follicle-stimulating hormone (FSH) value in the postmenopausal range upon pre-study (screening) evaluation
   c. 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, MRI, or CT scan. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must fulfill the criteria in Inclusion Criteria 5. Information must be captured appropriately within the site's source documents.
5. Female patients of childbearing potential (see above) must agree to use 1 highly effective form of contraception with their partners starting with the screening visit through 150 days after the last dose of study therapy

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6. Patient has an ECOG performance status of ≤ 2 for Part 1 and ≤ 1 for Part 2.
7. Patient has adequate organ function, defined as:
   a. Absolute neutrophil count (ANC) ≥ 1,500/μL
   b. Platelets ≥ 100,000/μL
   c. Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L
   d. Serum creatinine ≤ 1.5× upper limit of normal (ULN) or calculated creatinine clearance ≥ 50 mL/min using Cockcroft-Gault equation for patients with creatinine levels > 1.5× institutional ULN
   e. Total bilirubin ≤ 1.5× ULN AND direct bilirubin ≤ 1× ULN
   f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5× ULN unless liver metastases are present, in which case they must be ≤ 5× ULN
   g. International normalized ratio (INR) or prothrombin time (PT) ≤1.5× ULN unless patient is receiving anticoagulant therapy as long as PT or partial thromboplastin (PTT) is within therapeutic range of intended use of anticoagulants. Activated partial thromboplastin time (aPTT) ≤1.5× ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Main Criteria for Exclusion (Criteria apply to Part 1, 2A, and 2B):

Patients will not be eligible for study entry if any of the following criteria are met:

1. Patient has received prior therapy with an anti-programmed death-1 (anti-PD-1), anti-PD-1-ligand-1 (anti-PD-L1), or anti-PD-1 ligand-2 (anti-PD-L2) agent.
2. Patient has known uncontrolled central nervous system (CNS) metastases and/or carcinomatous meningitis. Note: Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are clinically stable off corticosteroids for at least 7 days prior to study treatment. Carcinomatous meningitis precludes a patient from study participation regardless of clinical stability. Patients with primary CNS tumors are eligible for Cohort F as long as they are neurologically stable in the absence of systemic corticosteroid use for at least 14 days prior to the first dose of study treatment.
3. Patient has a known additional malignancy that progressed or required active treatment within the last 2 years. Exceptions include basal cell carcinoma of the skin, squamous-cell carcinoma (SqCC) of the skin that has undergone potentially curative therapy, or in situ cervical cancer.
4. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease or active infection requiring systemic therapy. Specific examples include, but are not limited to, active, non-infectious pneumonitis; uncontrolled ventricular arrhythmia; recent (within 90 days) myocardial infarction; uncontrolled major seizure disorder; unstable spinal cord compression; superior vena cava syndrome; or any psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study (including obtaining informed consent).

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5. Patient is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study, starting with the screening visit through 150 days after the last dose of study treatment.
6. Patient has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
7. Patient has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
8. Patient has known active hepatitis B (e.g., hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (e.g., hepatitis C virus ribonucleic acid [HCV RNA] [qualitative] is detected).
9. Patient has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Use of inhaled steroids, local injection of steroids, and steroid eye drops are allowed.
10. Patient has a history of interstitial lung disease.
11. Patient has not recovered (i.e., to ≤ Grade 1 or to baseline) from radiation- and chemotherapy-induced AEs or received transfusion of blood products (including platelets or red blood cells) or administration of colony-stimulating factors (including granulocyte-colony stimulating factor [G-CSF], granulocyte macrophage colony-stimulating factor [GM-CSF] or recombinant erythropoietin) within 3 weeks prior to the first dose of study drug.
12. Patient has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks prior to the first dose of study drug.
13. Patient has received prior anticancer therapy (chemotherapy, targeted therapies, radiotherapy, or immunotherapy) within 21 days, or less than 5 times the half-life of the most recent therapy prior to study Day 1, whichever is shorter. Note: palliative radiation therapy to a small field ≥ 1 week prior to Day 1 of study treatment may be allowed.
14. Patient has not recovered adequately (≤ Grade 1) from AEs and/or complications from any major surgery prior to starting therapy.
15. Patient has received a live vaccine within 14 days of planned start of study therapy.
16. Patient has a known hypersensitivity to dostarlimab components or excipients.

Investigational Product(s), Dosage, and Mode(s) of Administration:

Dostarlimab (160 mg, 20 mg/mL; or 500 mg, 50 mg/ml) is administered via a 30 minute IV infusion (with a -5 minute and +15 minute window permitted) on Day 1 and Day 15 of each cycle in Part 1. For additional patients enrolled specifically to better characterize the PK/PDy profile in Part 1, dostarlimab administration during Cycle 1 will only occur on Day 1 with the second dose administered on Cycle 2/Day 1 and Q2W thereafter. For Part 2A and 2B, dostarlimab is administered on Day 1 of each treatment cycle.

Dosing in Part 2A will utilize 2 fixed-dose schedules of dostarlimab at 500 mg dostarlimab Q3W and 1000 mg dostarlimab Q6W.

For weight-based doses in Part 1, the dose will be calculated based on the weight obtained within the last 30 days prior to each treatment administration.

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Treatment cycles in Part 1 are 28 ± 3 days in duration, with the exception of Cycle 1 during Part 1, which is 28 ± 1 day, to accommodate PK sampling. In Part 2A and Part 2B, the duration of each treatment cycle is the time between each scheduled dose (i.e., a 21-day cycle for the Q3W cohort and a 42-day cycle for the Q6W cohort). The Study Manual contains specific instructions for the preparation of each dose and administration of the infusion solution. Part 1 and Part 2A were completed as of February 2017. Both fixed-dose schedules in Part 2A were determined as safe. The RP2D for dostarlimab was determined to be 4 cycles of 500 mg Q3W followed by 1000 mg Q6W for all subsequent cycles; this dosing schedule will be used in Part 2B.
Duration of Treatment: Planned Study Conduct Duration: 36 months (time from first patient enrolled until all patients have completed the study [last visit, last patient]). Planned Study Treatment Duration: Study treatment may continue for up to 2 years or until PD, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment beyond 2 years may be considered following discussion between the Sponsor and Investigator.

Criteria for Evaluation:
Safety:
• DLTs during Cycle 1
• Part 1: 28 days
  • Part 2A: 21 days for Q3W fixed-dose cohort
  • Part 2A: 42 days for Q6W fixed-dose cohort
• Incidence of treatment-emergent adverse events (TEAEs) and SAEs occurring while patients are on treatment or up to 90 days after end of treatment visit
• Changes in clinical laboratory parameters (hematology, chemistry, thyroid function, urinalysis), vital signs, ECOG performance status, ECG parameters, physical examinations, and usage of concomitant medications
Clinical Activity:
• Primary (antitumor activity in Part 2B):
  • dMMR/MSI-H endometrial patients and dMMR/MSI-H non-endometrial patients (patients in Cohorts A1 and F, respectively): ORR, defined as the proportion who have achieved CR or PR, evaluated using RECIST v1.1 based on independent blinded central review, and DOR, defined as the time from first documentation of CR or PR by RECIST v1.1 until the time of first documentation of PD evaluated using RECIST v1.1 based on independent blinded central review, or death due to any cause.
  • [redacted]

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[redacted]

- Secondary (Part 1):
  - irORR based on Investigators' assessment using irRECIST
- Secondary (Part 1 and Part 2):
  - Disease control rate (irDCR) based on Investigators' assessment using irRECIST
  - Duration of response (irDOR) based on Investigators' assessment using irRECIST
  - Progression-free survival (irPFS) based on Investigators' assessment using irRECIST
  - PFS based on independent blinded central review using RECIST v1.1 (Cohorts A1 [redacted]
  - Overall response rate (irORR) based on Investigators' assessment using irRECIST (Cohorts A1, [redacted])
  - Overall response rate (ORR) based on independent blinded central review using RECISTv1.1 in dMMR/MSI-H and POLE-mut cancers
  - Duration of response (DOR) based on independent blinded central review using RECISTv1.1 in dMMR/MSI-H and POLE-mut cancers
  - DCR based on Investigators' assessment using RECIST v1.1 (Cohorts A1, [redacted])
  - OS, as measured from the date of first dose to the date of death by any cause

<u>Pharmacokinetics/Pharmacodynamics:</u>

- PK: Serum PK analysis to assess AUC, minimum concentration (C_{min}), maximum concentration (C_{max}), clearance (CL), volume of distribution (Vz), AUC at steady state (AUC_{ss}), C_{min} at steady state ($C_{min,ss}$), and C_{max} at steady state ($C_{max,ss}$)
- Immunogenicity: Serum samples for analysis of anti-dostarlimab antibodies (all the predose samples, and at/after 96 hours samples relative to each dose including safety follow up samples).

<u>Biomarkers:</u>

- Blood-based biomarkers may include serum cytokines, circulating immune cells, and circulating tumor cells
- Tumor-based biomarkers may include description of immune cells, gene expression profiling, and/or measurement of protein levels for immune-related and tumor-related proteins and

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assessment of tumor genome for mutations and/or alterations (e.g., MMR/MSI and POLE mutations)

Statistical Methods:
Sample Size Considerations

Sample size calculations were performed using SAS® version 9.4.

Part 1: A total sample size of approximately 36 patients is expected, but this may increase to approximately 54 patients, for the dose escalation portion of the study to provide incidence of DLTs as well as the safety and PK/PDy profile of dostarlimab.

Part 2A: A total sample size of approximately 12 patients is expected, but this may increase up to 24 patients, depending on the number of DLTs observed.

Part 2B: A total sample size of up to 680 patients is estimated for the expansion portion of this study to provide assessment of clinical activity of dostarlimab based on ORR.

For Cohort A1 in Part 2, the null hypothesis that the true response rate is ≤20% (H_0: p≤ 0.2) will be tested against a one-sided alternative of ≥40% (H_a: p≥ 0.4). With 65patients treated, the cohort has 92% power to rule out a ≤ 20% ORR (null hypothesis) when the true ORR is 40% at the 2.5% type I error rate (one-sided).

The sample size of Cohort A1 will be increased to 100 patients which will allow the lower-limit boundary of the exact 95% confidence interval (CI) excluding a response rate of 25% or less and assuming observed ORR is 35%.

[redacted]

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[redacted]

Analysis Populations

Four analysis populations will be defined:

- Safety Population (SAF): All patients who receive any amount of study drug.

  For dose escalation decision purposes, the assessment of DLTs will include:

  - Part 1: Only those patients who received 2 doses of dostarlimab (i.e., on Cycle 1/Day 1 and Cycle 1/Day 15) and completed the safety evaluations throughout Cycle 1 (i.e., 28 days) or patients who discontinued study drug during Cycle 1 due to a DLT.
  - Part 2A: Only those patients who received one dose of dostarlimab and completed the safety evaluations throughout Cycle 1 (i.e., 21 days for the Q3W cohort and 42 days for the Q6W cohort) or patients who discontinued study drug during Cycle 1 due to a DLT
- Efficacy Population:
  - Part 1 and Part 2A: All patients who received any amount of study drug.
  - dMMR/MSI-H EC patients from Cohorts A1 as well as retrospectively identified dMMR EC patients from Cohort A2 in Part 2B: All patients in Safety Population with measurable disease at baseline (defined as the existence of at least one target lesion) have dMMRstatus based on MMR testing result using IHC (local or central) OR MMR status unknown with MSI-H based on local or central MSI testing results using PCR or NGS.
  - MMR-proficient/MSS EC patients from Cohorts A2 as well as retrospectively identified MMR-proficient EC patients from Cohort A1 in Part 2B: All patients in Safety Population with measurable disease at baseline (defined as the existence of at least one target lesion) who have MMR-proficient status based on MMR testing result using IHC (local or central) OR MMR status unknown with MSS based on local or central testing results using PCR or NGS.
  - [redacted]

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- [redacted]
- Per Protocol Population (PP): All patients in the Efficacy Population who have measurable disease at baseline and have no significant protocol deviations during the study.
- PK Population: All patients who receive at least 1 dose of study drug and have at least 1 PK sample.
- Antidrug-Antibody (ADA) population: All patients who receive at least 1 dose of study drug, have provided the pre-treatment blood sample and at least 1 post-treatment serum sample at or after 96 hours.
- PRO population: All patients in Cohorts A1 and F enrolled under Amendment 3 or subsequent amendments, who have completed both baseline and at least 1 post-baseline PRO assessment.

General Methods

All analyses will be performed based on dMMR/MSI-H, MMR-proficient/MSS, and MMR unknown and will include summary statistics, including number and percentage for categorical variables, and the number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided 95% CIs will be provided where appropriate. Time-to-event analyses will be performed using Kaplan-Meier methods. Further details will be provided in the study statistical analysis plan (SAP).

Safety

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) for purposes of summarization. All AEs occurring during the study will be included in by-patient data listings and tabulated by MedDRA system organ class and preferred term. Safety endpoints for AEs include the following: incidence of DLTs, TEAEs, immune-related adverse events (irAEs), TEAEs leading to death, SAEs, and AEs leading to discontinuation. Tabulations of TEAEs will also be produced by severity and by relationship to study drug

Additional safety summaries will be provided for clinical laboratory tests, vital signs, ECOG performance status, and ECGs.

Clinical Activity

Preliminary clinical activity will be assessed. ORR, irORR, DCR, and irDCR will be listed and summarized by dose (if applicable) or cohort using descriptive statistics including the number, percentage, and 2-sided 95% CIs. Actual values and changes from baseline in tumor burden will be summarized by time-point.

DOR, irDOR, PFS, irPFS, and OS will be summarized using Kaplan-Meier analysis, including number and percentage of events, number and percentage of censored patients, and 25^{th}, 50^{th} (median), and 75^{th} percentiles of times-to-event with 2-sided 95% CIs for the median.

Actual values and change from baseline in PRO assessments (EQ-5D-5L and EORTC-QLQ-C30) scored according to each instrument's scoring manual will be summarized by time point.

Pharmacokinetics/ADA/Pharmacodynamics

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Serum concentrations, PK parameters, PDy parameters, and ADA data will be summarized with descriptive statistics by study phase, dose, and regimen. ***Biomarkers*** The incidence/changes of biomarkers will be summarized using descriptive statistics. Comparisons of clinical activity between biomarker subpopulations may be performed.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
ALC	absolute lymphocyte count
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-PD-1	anti-programmed death-1
anti-PD-L1	anti-programmed death-1-ligand-1
anti-PD-L2	anti-programmed death-1-ligand-2
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0\text{-}LAST}$	area under the concentration-time curve from time 0 to last assessment
$AUC_{0\text{-}\infty}$	area under the concentration-time curve from time 0 to infinity
AUC_{ss}	area under the concentration-time curve at steady state
BP	blood pressure
C	cycle
CA-125	cancer antigen 125
CBC	complete blood count
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
$C_{max,ss}$	maximum concentration at steady state
C_{min}	minimum concentration
$C_{min,ss}$	minimum concentration at steady state
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CT	computed tomography

Abbreviation	Definition
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
COPD	chronic obstructive pulmonary disease
C_{trough}	trough concentration
CV	coefficient of variation
D	day
DCR	disease control rate
DL	dose level
DLT	dose-limiting toxicity
dMMR	mismatch repair deficient
DNA	deoxyribonucleic acid
DOR	duration of response
EC	endometrial cancer
ECG	electrocardiogram
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EORTC	European Organization for Research and Treatment of Cancer
EOT	end-of-treatment
EQ VAS	EQ Visual Analog Scale
EQ-5D-5L	European Quality of Life scale, 5-Dimensions
EU	European Union
FSH	follicle-stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBsAg	hepatitis B surface antigen
HCV RNA	hepatitis C virus ribonucleic acid

Abbreviation	Definition
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	immunohistochemistry
INR	international normalized ratio
irAE	immune-related adverse events
irAEI	immune-related adverse events of interest
IRB	Institutional Review Board
irCR	immune-related complete response
irDCR	immune-related disease control rate
irDOR	immune-related duration of response
irORR	immune-related objective response rate
irPFS	immune-related progression-free survival
irPR	immune-related partial response
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
irSD	immune-related stable disease
IUD	intrauterine device
IV	intravenous(ly)
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MMR	DNA mismatch repair
MMR-proficient	mismatch repair proficient
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability high
MSS	microsatellite stable
MTD	maximum tolerated dose
NAb	neutralizing antibody

Abbreviation	Definition
NCCN	National Comprehensive Cancer Network
NGS	next-generation sequencing
NSAID	non-steroidal anti-inflammatory drug
[redacted]	[redacted]
OC	ovarian cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death ligand-1
PD-L2	programmed death ligand-2
PDy	pharmacodynamic
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PO	by mouth
POLE	polymerase
POLE-mut	polymerase ε mutated
PP	per protocol population
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
QLQ	quality of life questionnaire
QoL	quality of life
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose

Abbreviation	Definition
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
SqCC	squamous-cell carcinoma
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocytes
TKI	tyrosine-kinase inhibitor
TSH	thyroid-stimulating hormone
US	United States
ULN	upper limit of normal
V_z	volume of distribution

1. INTRODUCTION

1.1. Background

The recognition of tumors by the immune system has been appreciated for multiple decades and provided an impetus to utilize the immune system to control tumor growth. Studies have reported the presence of tumor-infiltrating lymphocytes (TILs) as a positive prognostic feature in multiple tumors supporting a role for the immune system in limiting tumor growth.[1-3] Despite evidence of immune reactivity, tumors are able to grow in the presence of an immune system suggesting a suboptimal immune response.

Initial exploration of T cell activation in chronic viral models suggested that chronic viral infections lead to a state of T cell hypo-responsiveness, termed T cell exhaustion, and involved immune inhibitory receptors expressed by T cells.[4,5] One of the proteins shown to be mediating T cell exhaustion in chronic viral models and subsequently tumor models was programmed cell death-1 (PD-1). The discovery and characterization of PD-1 revealed that PD-1 limits T cell activation through binding to PD-L1 and PD-L2 and limiting tyrosine kinase signaling from the T cell antigen receptor and co-stimulatory receptors.[6,7]

The identification of PD-L1 as the ligand for PD-1 was followed by the demonstration that PD-L1 expression by tumor cells enhances tumor growth.[8] These data led to the hypothesis that PD-1/L1 may be exploited to subvert the antitumor immune response. Preclinical models where PD-1 signaling was blocked or deficient (PD-1 knockout mice) demonstrated improved immune-mediated tumor control.[8,9] Thus, PD-1/PD-L1 represented an immune inhibitory mechanism employed by tumors to subvert the immune response and disruption of this axis enhanced the lysis of tumor cells by T cells.

These preclinical experiments led to the evaluation of anti-PD-1 antibodies in patients with solid tumors. From the first clinical study, the activity of an anti-PD-1 antibody, nivolumab, appeared to be enhanced compared to past immunotherapeutic approaches.[10] Activity was demonstrated in tumors known to be responsive to immunotherapy, i.e., melanoma and renal cell carcinoma (RCC), as well as lung tumors which were traditionally insensitive to immunotherapy, i.e., non-small cell lung cancer (NSCLC). This led to intense interest in PD-1/PD-L1 blockade in multiple tumor types resulting in the development of specific antibodies that block PD-1 or PD-L1 that have subsequently demonstrated clinical efficacy in multiple malignancies.

Multiple clinical trials in various cancer types have yielded positive data with a number of different antibodies targeting PD-1. For example, nivolumab has received approvals in the US and EU for the treatment of patients with melanoma, NSCLC, urothelial carcinoma, RCC, classical Hodgkin lymphoma, and head and neck squamous cell carcinoma (HNSCC)[11,12] as well as microsatellite instability high (MSI-H) colorectal cancer (CRC) (US).[11] Similarly, pembrolizumab has been approved in the US and EU for treatment of patients with melanoma, NSCLC, classical Hodgkin lymphoma, urothelial carcinoma.[13,14] In the US, pembrolizumab has also been approved for the treatment of patients with head and neck squamous cell cancer and unresectable or metastatic MSI-H cancer.[13] In addition, the anti-PD-L1 antibody, durvalumab, has been approved in the US for the treatment of patients with advanced or metastatic urothelial carcinoma.[15] Although nivolumab, pembrolizumab, and durvalumab are distinct antibodies, the safety profiles are very similar across therapies and across tumor types demonstrating that the

targeting of PD-1/PD-L1 pathway was well-tolerated with manageable immune-related adverse events (irAEs) being the most noteworthy.

1.2. Dostarlimab

The broad spectrum of cancers amenable to PD-1 blockade supports the value of developing an antibody that targets PD-1 to utilize as a single agent and in combination with other therapeutic approaches. Dostarlimab (formerly referred to as TSR-042) is an IgG4-k 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 antibodies with desired functional characteristics. The functional antagonist activity of dostarlimab was confirmed in a mixed lymphocyte reaction (MLR) demonstrating enhanced interleukin-2 production upon addition of dostarlimab. Furthermore, dostarlimab has an acceptable safety profile based on toxicology studies in cynomolgus monkeys. Based on the dostarlimab preclinical data, dostarlimab is expected to result in similar clinical benefit in patients with a variety of tumors with results similar to antibodies of the same class (nivolumab and pembrolizumab) and thus dostarlimab is being evaluated clinically as an immunotherapy for advanced malignancies.

1.2.1. Rationale for Current Trial

The objectives of this trial include determining a safe and efficacious dose of dostarlimab. Part 1 of the study will evaluate ascending weight-based doses of dostarlimab based on dose-limiting toxicities (DLTs), overall safety, and the pharmacokinetic (PK)/pharmacodynamic (PDy) profile. The starting dose of dostarlimab (i.e., 1 mg/kg) was selected based on the results of the animal toxicology studies (see Investigator Brochure for details), as well as the reported safety profile of multiple anti-PD-1 antibodies from patients treated with a range of doses.[16-22]

Part 2A will evaluate safety and tolerability of dostarlimab at a flat-fixed dose, which will be derived from safety and tolerability data and PK/PDy profile of weight-based doses tested in Part 1.

Part 2B of the study will explore initial signs of efficacy in pre-specified tumor types using the recommended Phase 2 dose (RP2D) determined from Part 1 and 2A. The tumors to be explored in the expansion cohorts represent multiple tumor types where immune control of neoplastic transformation is suppressed in part by PD-1 receptor-ligand interactions.

1.2.2. Rationale for Endometrial Cancer Cohorts

Endometrial cancer is divided into 2 types: Type I comprises endometrioid cancer and Type II includes serous and clear cell histologies. The majority of localized endometrial cancer is treated with surgery and radiation; however, a subset of patients recur or present with metastatic disease, and median OS is 12 to 15 months in these patients. Chemotherapy for first-line therapy consists of carboplatin and paclitaxel, whereas there is no approved treatment or standard of care for patients who progress following first-line therapy. Thus, second-line treatment for recurrent or advanced endometrial cancer is an area of unmet medical need.

Comprehensive genomic and transcriptomic analysis of endometrial cancers have defined a subgroup of tumors that present with a high frequency of somatic mutations that are attributable to defects in mismatch repair.[23] The DNA mismatch repair (MMR) system is made up of four

essential proteins that are involved in identifying and initiating repair of DNA base pair mismatches. When the MMR system develops functional errors or defects, this results in a particular phenotype called microsatellite instability (MSI).[24] Comprehensive genomic and transcriptomic analysis of endometrial cancers have defined a subgroup of tumors that present with a high frequency of somatic mutations that are attributable to defects in MMR and are considered MSI-high (MSI-H).[23] A common and established method to categorize tumors and to test for the presence of the MSI-H phenotype is by assessing the expression of the four MMR proteins using an immunohistochemistry (IHC) assay. Loss of expression of at least 1 MMR protein in this assay will result in the tumor being called dMMR with a phenotype of MSI-H.

Tumors in this group, MSI-H endometrial cancers, are characterized by an active immune microenvironment evidenced by the abundance of tumor-specific neoantigens and a high number of tumor infiltrating lymphocytes,[25] factors that have been shown to correlate with response to checkpoint inhibition. In this context, responses to therapies that target immune checkpoint molecules, such as PD-1, appear to correlate both with the frequency of somatic tumor mutations and lymphocyte infiltration, suggesting that MSI-H endometrial cancer patients treated with dostarlimab may receive benefit. Of note, aggregate data from clinical trials of the anti-PD-1 antibody, pembrolizumab, in MSI-H cancers showed that 5 of 14 patients with MSI-H endometrial carcinoma achieved a clinical response (ORR 36% with 95% CI [13%, 65%]; DOR range 4.2+ to 17.3+ months).[26]

Additionally, the KEYNOTE-028 study, which enrolled recurrent and advanced endometrial cancer patients whose tumor cells expressed PD-L1 reported overall response rate of 13% (N=3/23), median PFS of 1.8 months, and 12 months OS rate of 51%, with median OS not reached at the time of data cut off.[27] The study enrolled patients regardless of their tumor MSI status and these data suggest that the broader population of endometrial patients may benefit from anti-PD-1 directed therapy.

Based on these data, the study will enroll 2 separate endometrial cancer cohorts to allow the study of the overall treatment effect of dostarlimab in recurrent disease and also to understand the role of MMR status and its phenotype, MSI in response to treatment with dostarlimab. IHC is routinely used to assess dMMR in endometrial cancer patients as a test for Lynch syndrome and preliminary results from Cohort A1 showed that all responders were dMMR (and therefore an MSI-H phenotype) by IHC. There was a subgroup of patients, initially identified as dMMR/MSI-H by IHC who could not be confirmed by central NGS testing. Consequently, to ensure that all responders to dostarlimab are categorized by their appropriate cohort: Cohorts A1, [redacted] the Sponsor decided to select dMMR/MSI-H or MMR-proficient/MSS by IHC test.

1.2.3. [redacted]

[redacted]

In summary, treatment options for patients with recurrent/advanced disease of the types selected for this study who have recurrent or progressive disease (PD) after the 1st line of systemic therapies are limited.[28-32] Given that clinical activity of antibodies targeting the PD-1 axis have been observed in a broad range of solid tumors, the patients with disease types selected for evaluation in this study are expected to derive clinical benefit. This study will determine the safe and tolerable dose of dostarlimab to provide preliminary information related to the extent of clinical benefit in patients with selected tumor types in the dostarlimab expansion cohorts.

1.2.4. Rationale for Non-Endometrial MSI-H or POLE-mutated Cancer Cohort

High-frequency microsatellite instability (MSI-H) is not unique to endometrial cancer and can be identified in other solid tumor types including colorectal, gastric, NSCLC, and ovarian cancers.[33-35] MSI-H arises from a failure to repair replication-associated errors due to a defective DNA mismatch repair (MMR) system. This failure allows persistence of mismatch mutations all over the genome, but especially in regions of repetitive DNA known as microsatellites. Persistent mismatch mutations, leading to increased mutational burden, have been demonstrated to improve responses to anti-PD-1 agents.[36,37] In addition, tumors with increased mutational burden and tumors with MSI-H have been reported to have upregulation of immune checkpoints, including PD-1 and PD-L1, suggesting they may be amenable to anti-PD-1 directed immunotherapy.[38-43] This hypothesis has been validated by the recent accelerated approval in the US of pembrolizumab for treatment of MSI-H tumors. This approval was based on data pooled from 5 clinical trials, across 149 patients spanning 15 tumor types in which ORR was 39% with associated 95% confidence interval of (32%, 48%) and DOR ranging from 1.6+ to 22.7+ months.[13]

A recent report from Le et al (2017)[44] evaluated 12,019 cancers representing 32 distinct tumor types for MMR-deficiency using a next generation sequencing (NGS) approach. In this study, >5% of adenocarcinoma of the endometrium, stomach, small intestine, colon and rectum, cervix, prostate bile duct and liver as well as neuroendocrine tumours, non-epithelial ovarian cancers and uterine sarcomas were MMR deficient. A subset of those patients meet the criteria of having recurrent or advanced microsatellite instability-high (MSI-H) solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Patents with Polymerase ε (POLE) mutations will also be included in this cohort. POLE is a nuclear depolymerase with intrinsic proofreading activity that is important in ensuring the fidelity of DNA replication.[45] Mutations in the exonuclease domain of POLE are associated with dramatic increases in spontaneous mutations and an ultra-mutated phenotype with high mutational burden.[46] Importantly, it appears that most POLE mutated patients are MSI stable and are not recognized by established IHC or PCR-based tests used for the detection of microsatellite instability.[45,47] However, POLE mutations can be detected using next generation sequencing and anti-tumor activity of anti-PD-1 agents in these tumors has been reported.[48,49]

Assessment of these genetic subsets may lead to further understanding of the clinical benefit anticipated by new immunotherapies, including dostarlimab.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objectives of this study are as follows:

Part 1 – Dose Escalation Cohorts:

- To evaluate the safety and tolerability of dostarlimab in patients with advanced solid tumors and determine the recommended RP2D and schedule

Part 2A – Fixed-Dose Safety Evaluation Cohorts

- To evaluate the safety and tolerability of dostarlimab at fixed-dose in patients with advanced solid tumors and determine the RP2D and schedule

Part 2B – Expansion Cohorts:

- Cohorts A1 [redacted] To evaluate the antitumor activity of dostarlimab in patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) cancers, including dMMR/MSI-H endometrial cancer (Cohort A1) [redacted], in terms of objective response rate (ORR) and duration of response (DOR) by independent blinded central review using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- [redacted]
- [redacted]

2.2. Secondary Objectives

The secondary objectives of the study are as follows:

Part 1 – Dose Escalation Cohorts:

- To evaluate irORR as assessed by the Investigators using irRECIST

Part 1 and Part 2:

- To characterize the PK profile of dostarlimab
- To evaluate the immunogenicity of dostarlimab
- To evaluate additional measures of clinical benefit, including:
  - Immune-related disease control rate (irDCR) based on Investigators' assessment using irRECIST
  - Immune-related duration of response (irDOR) based on Investigators' assessment using irRECIST

- Immune-related progression-free survival (irPFS) based on Investigators' assessment using irRECIST
- Progression-free survival (PFS) based on independent blinded central review using RECIST v1.1 (Cohorts A1, [redacted])
- Immune-related overall response rate (irORR) based on Investigators' assessment using irRECIST (Cohorts A1, A2, and F)
- Overall response rate (ORR) based on independent blinded central review using RECISTv1.1 in dMMR/MSI-H and POLE-mut cancers
- Duration of response (DOR) based on independent blinded central review using RECISTv1.1 in dMMR/MSI-H and POLE-mut cancers
- Disease control rate (DCR) based on Investigators' assessment using RECIST v1.1 (Cohorts A1, [redacted])
- Overall survival (OS)

2.3. Exploratory Objectives

The exploratory objectives of the study are as follows:

- To characterize the pharmacodynamic (PDy) profile of dostarlimab
- To explore changes in intratumoral cells and circulating biomarkers in the blood following treatment with dostarlimab
- To explore the profile of tumor-infiltrating lymphocytes (TILs), tumor cell characteristics including genomic alterations (e.g., MMR/MSI and POLE), and/or circulating biomarkers prior to treatment with dostarlimab and correlate with clinical benefit.
- Patient-reported outcomes (PROs) [European Quality of Life scale, 5-Dimensions (EQ-5D-5L) and European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30)] in patients in Cohorts A1 [redacted] enrolled under Amendment 3 or subsequent amendments

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

3.1.1. Overview

This is a multicenter, open-label, first-in-human, Phase 1, dose escalation study with expansion cohorts designed to assess the safety, PK, PDy, and clinical activity of the anti-PD-1 antibody, dostarlimab, in patients with advanced solid tumors who have limited available treatment options as determined by the Investigator. The study will be conducted in 2 parts: Part 1 will evaluate safety, PK, and PDy of escalating doses of dostarlimab and Part 2 will further evaluate the safety and clinical activity of dostarlimab in cohorts of patients with specific types of advanced solid tumors.

Part 1 (dose escalation) will initially evaluate 3 ascending weight-based dose levels (DLs) of dostarlimab, 1 mg/kg, 3 mg/kg and 10 mg/kg, administered via intravenous (IV) infusion using a modified 3+3 design. Further dose escalation to 15 mg/kg or 20 mg/kg (not to exceed 20 mg/kg) may also be assessed in an additional cohort following agreement between the Investigators and Sponsor.

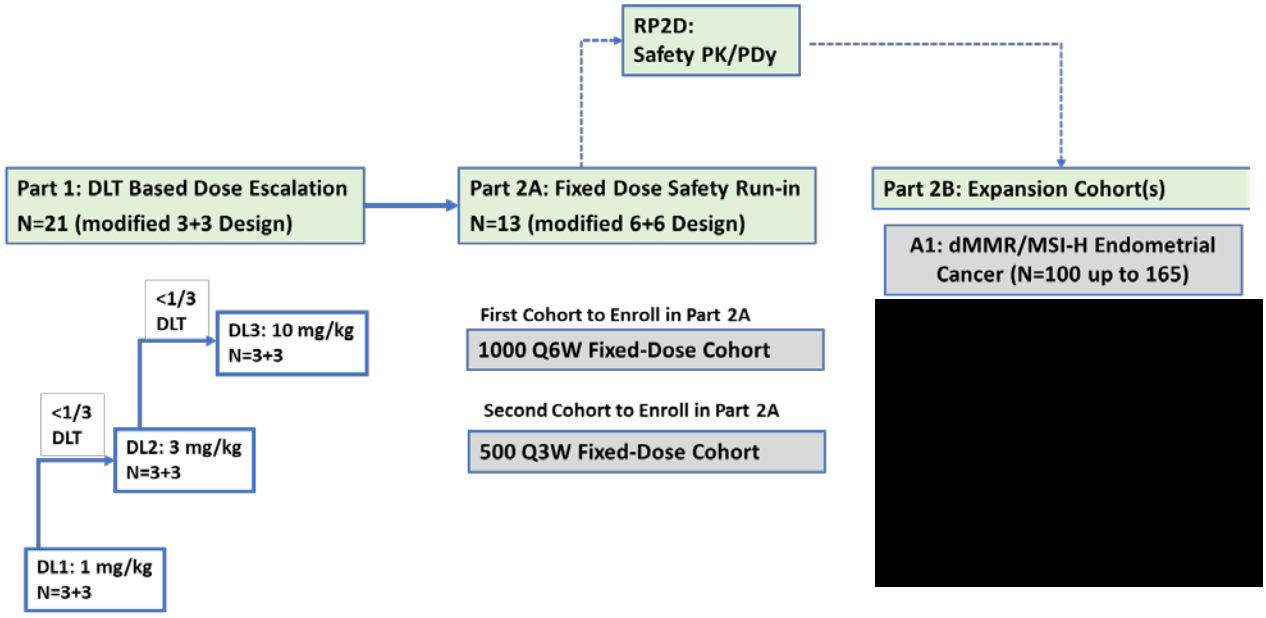
In Part 2, the study will be conducted in two subparts, Part 2A (fixed-dose safety evaluation cohorts) and Part 2B (expansion cohorts). Part 2A of the study will evaluate the safety and tolerability of dostarlimab at fixed doses of 500 mg administered every 3 weeks (Q3W) and 1000 mg administered every 6 weeks (Q6W). Part 2B of the study will examine clinical activity of dostarlimab in selected tumor types.

As of February 2017, Part 1 and Part 2A of this study were completed. Both fixed doses tested in Part 2A were found to be safe. The RP2D, determined by the Sponsor following an evaluation of multiple endpoints, including the DLT rate in Part 1 and Part 2A, safety and tolerability over all cycles in both parts of the study, and the PK and/or PK/PDy profile, was determined to be 500 mg dostarlimab Q3W for the first 4 cycles, followed by 1000 mg TSR042 Q6W for all subsequent cycles.

Figure 1 presents an overview of the planned study schema. The schedules of events for the study are provided in Table 3 (Part 1) and Table 4, Table 5, and Table 6 (Part 2B).

The study will be conducted in conformance with Good Clinical Practice (GCP).

Figure 1: Study Schema[a]



Abbreviations: Abbreviations: DL=dose level; DLT=dose-limiting toxicity; dMMR= mismatch repair deficient; MSI-H=microsatellite instability high; MMR-proficient=mismatch repair proficient; MSS=microsatellite stable; [redacted]; N or n=number (of patients); POLE-mut=polymerase ε mutated; Q3W=every 3 weeks; Q6W=every 6 weeks; RP2D=recommended Phase 2 dose;
[a] Adjustments to enrollment within cohorts may occur based on emerging data and Sponsor's decision.

3.1.2. Part 1 Dose Escalation

Part 1 will be conducted using a modified 3+3 design with a plan to evaluate 3 ascending weight-based DLs of dostarlimab, 1 mg/kg, 3 mg/kg, and 10 mg/kg, via IV infusion in 28-day cycles. Further dose escalation to 15 mg/kg or 20 mg/kg (not to exceed 20 mg/kg) may be assessed in an additional cohort(s) following agreement between the Investigators and Sponsor. Patients enrolled in Part 1 for DLT-based dose escalation will begin treatment with dostarlimab administered on Cycle 1/Day 1 and Cycle 1/Day 15 followed by on-treatment visits throughout the first cycle (i.e., 28 days) for safety assessments and blood sampling for PK/PDy. In all subsequent cycles, doses of dostarlimab will be administered on Day 1 and Day 15.

To better characterize the PK/PDy profile of dostarlimab, additional patients (up to 6 patients per DL) may subsequently be enrolled at a DL with DLTs observed in <33% of patients. These patients will begin treatment with dostarlimab on Cycle 1/Day 1 followed by on-treatment visits during the following 28 days for safety assessments and blood sampling for PK/PDy (i.e., no dostarlimab treatment on Cycle 1/Day 15). Starting with Cycle 2, dostarlimab will be administered on Day 1 and Day 15 in all subsequent cycles.

Cohorts will be enrolled sequentially with DL1 (1 mg/kg) being the first cohort to enroll 3 patients. Dose escalation or expansion to 6 patients will be considered after all 3 patients in DL1 have completed Cycle 1 of treatment and determined by the Investigators and Sponsor to be evaluable upon review of safety data. A patient will be considered non-evaluable if, for any reason other than safety, the patient is unable to complete the DLT observation period (Cycle 1,

Days 1 to 28). Patients in Part 1 considered non-evaluable may be replaced after consultation between the Investigators and Sponsor.

If, after 3 patients are enrolled there are no DLTs observed (see Section 5.2 for the definition of DLT) in any of the 3 patients through the DLT observation period (i.e., through Cycle 1/Day 28), then the next higher dose cohort will open for enrollment. If 1 of the first 3 patients experiences a DLT, then 3 additional patients will be enrolled (total of 6 evaluable patients at the same DL). No further dose escalation will be considered if DLTs are observed in 2 or more of 6 evaluable patients.

Dose escalation will continue until the maximum tolerated dose (MTD) is reached or may be stopped at any dose level up to the highest dose of 20 mg/kg based on emerging safety and PK/PDy data, subject to agreement between the Investigators and Sponsor. The MTD will be defined as the dose level -1 of the dose level that is found to be unsafe based on a modified 3+3 design and have confirmed DLT rate <33% from at least 6 patients during Cycle 1 of treatment.

Patients in Part 1 may continue treatment with dostarlimab for up to 2 years unless specific withdrawal criteria are met (Section 4.3). Continued treatment with dostarlimab beyond 2 years may be considered following discussion between the Investigators and Sponsor.

3.1.3. Part 2A Fixed Dose Safety Evaluation

A modified 6+6 design will be used to evaluate safety and tolerability of dostarlimab at fixed-dose levels of 500mg Q3W and 1000mg Q6W. Each cohort will enroll 6 patients and enrollment for the Q6W cohort will begin first followed by enrollment in the Q3W cohort. The cycle durations and DLT observation period are 21 days for the Q3W cohort and 42 days for the Q6W cohort. Patients in each cohort will receive dostarlimab via IV infusion on Day 1 of every cycle.

If ≤ 1 patient experiences DLT out of 6 evaluable patients in each cohort, the respective dose will be declared safe. If ≥ 2 patients experience DLT in any cohort, then 6 additional patients will be enrolled in that particular cohort. Here, if ≤ 3 patients out of 12 evaluable patients in the cohort experience DLT, then the respective dose will be considered safe. If ≥ 33% of evaluable patients experience DLT at any time in any cohort, the dose will be considered unsafe and enrollment in the cohort will stop.

A patient participating in Part 2A will be considered non-evaluable if, for any reason other than safety, the patient is unable to complete the DLT observation period (21 days for Q3W cohort, 42 days for Q6W cohort). Patients considered non-evaluable in Part 2A may be replaced after consultation between the Investigator and Sponsor.

If both Q3W and Q6W doses are determined to be safe, patients enrolled in the Q3W cohort are permitted to change to Q6W study treatment after having received at least 4 dostarlimab doses (i.e., 4 treatment cycles) in Part 2A.

Patients in Part 2A may continue treatment with dostarlimab for up to 2 years unless specific withdrawal criteria are met (Section 4.3).

3.1.4. Part 2B Expansion

Patients in Part 2B will be treated with RP2D determined based on data from Part 1 and 2A. Both fixed doses tested in Part 2A were determined as safe. Patients in Part 2B will receive

dostarlimab 500 mg every 3 weeks (Q3W) for the first 4 cycles followed by 1000 mg every 6 weeks (Q6W) for all subsequent cycles.

In Part 2B, Cohort A1 will enroll approximately 100 with the potential for up to 165 patients with dMMR/MSI-H EC,

Patients with one of the tumor types below are planned to be included:

- Cohort A1 - Patients with dMMR/MSI-H endometrial cancer who have progressed on or after platinum doublet therapy. Patients have received no more than 2 lines of anti-cancer therapy for recurrent or advanced (Stage ≥ IIIB) disease.
-

[redacted]

- Tumor MMR/MSI status: Patients can be screened based on local MMR/MSI testing results using immunohistochemistry (IHC), polymerase chain reaction (PCR), or next generation sequencing (NGS) performed in a certified local laboratory, but patient eligibility needs to be determined by MMR IHC results. For patients with available local MMR IHC results for the respective cohort(s), tumor samples have to be submitted to a central IHC laboratory and its quality has to be checked and cleared prior to C1D1. For patients without available local MMR IHC test results (patients with local PCR or NGS test results), tumor samples have to be submitted directly to central IHC laboratory and central IHC results have to confirm eligibility prior to proceeding with other screening procedures. After the central IHC test is completed, remaining tumor tissue may be sent to a central NGS laboratory for further testing.
- For POLE status: Patients who are considered for the study based on POLE mutation must have local results available showing tumor mutation(s) in the exonuclease domain of the POLE gene (amino acid residues 268-471) to begin screening. Patients must have the quality of submitted tumor samples checked and cleared by a central IHC laboratory prior to receiving study treatment.

Patients in Part 2B may continue treatment with dostarlimab for up to 2 years unless specific withdrawal criteria are met (Section 4.3). Continued treatment with dostarlimab beyond 2 years may be considered following discussion between the Investigator and Sponsor.

3.1.5. General Study Conduct: Part(s) 1 and 2

Following informed consent, patients in Part 1 will undergo screening procedures within 21 days, prior to the first dose of study treatment to determine eligibility for study entry. Patients in Part 2 will undergo screening procedures within 35 days prior to the first dose of study treatment. Screening procedures include medical, surgical, cancer, and medication history; complete physical examination, including vital signs, height, and weight; electrocardiogram (ECG); Eastern Cooperative Oncology Group (ECOG) performance status; and clinical laboratory tests, including complete blood count (CBC) with differential (including absolute lymphocyte count [ALC] and absolute neutrophil count [ANC]), coagulation, chemistry, thyroid panel (thyroid-stimulating hormone [TSH], triiodothyronine [T3] or free T3 [FT3], free thyroxine [FT4], or equivalent tests), urinalysis, tests for hepatitis B and C virus (when medically indicated), and pregnancy test.

Patients enrolled in Part 2B are required to have tumor tissue available (archival or newly obtained biopsy) prior to start of study treatment for assessment of the tumor microenvironment for exploratory biomarkers, including, but not limited to immune cells and immune-related proteins. In addition to these exploratory assessments, in cohorts A1, A2, and F of Part 2B, tumor tissue will be used for MMR/MSI and POLE testing. For patients in Part 2B who do not have archival tissue, a new biopsy must be performed to obtain a tissue sample prior to study treatment initiation.

Patients are enrolled based on local MMR/MSI testing results using immunohistochemistry (IHC), polymerase chain reaction (PCR), or next generation sequencing (NGS) performed in a certified local laboratory. All patients must submit tumor tissue block to a central IHC laboratory. Patients with available MMR/MSI-H results based on local testing must have the quality of submitted tumor tissue checked and cleared by a central IHC laboratory prior to receiving study treatment. For patients without available local MMR/MSI-H test results, results from a central IHC test have to confirm eligibility prior to receiving study treatment. After the central IHC test is completed, remaining tumor tissue may be sent to a central NGS laboratory for further testing.

Patients who are considered for the study based on POLE mutation must have local results available showing tumor mutation(s) in the exonuclease domain of the POLE gene (amino acid residues 268-471) to begin screening. Patients must have the quality of submitted tumor samples checked and cleared by a central IHC laboratory prior to receiving study treatment.

In patients who consent to optional serial biopsies, these biopsies will be obtained prior to initiation of study treatment (screening biopsy), 8-12 weeks (for Part 1) or approximately 4-6 weeks (for Part 2) after initiating study treatment and, whenever possible, at the time of PD (note: while the biopsies are voluntary, they are highly encouraged). A core biopsy is recommended (details are provided in the Study Manual); if an excisional or incisional biopsy is to be performed, it must be conducted on a non-target lesion. If a patient has had a biopsy prior to screening and within 12 weeks of study treatment, that biopsy may be accepted as the screening biopsy.

Radiographic evaluations (CT [preferred method] or MRI [if clinically indicated]) of the chest, abdomen, and pelvis must be conducted at screening to determine extent of disease and confirm presence of measurable disease (Part 2B patients). Appropriate testing of serum-based tumor markers, where applicable (e.g., CA-125 for OC patients), should also be conducted at screening. Brain scans will be conducted if clinically indicated. Bone scans will be conducted per standard of care. Scans performed prior to the signing of the informed consent form (ICF) as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and are performed within 28 days (± 3 days) prior to first dose date.

All patients will begin treatment on Cycle 1/Day 1. Safety assessments conducted throughout the treatment period include symptom-directed physical examination, vital signs, ECGs, ECOG performance status, and clinical laboratory assessments (CBC [with differential, including ALC and ANC], coagulation [per standard of care for patients on anticoagulant therapy], chemistry, thyroid panel [i.e., TSH, T3 or FT3, FT4, or equivalent tests], urinalysis, and pregnancy testing).

In Part 1, radiographic evaluations (CT/MRI of chest, abdomen, and pelvis) and appropriate testing of serum-based tumor markers to assess extent of disease will be conducted every 10 weeks (±10 days). After 1 year of radiographic assessments, patients will have imaging performed every 12 weeks (84 ±10 days). In Part 2A and Part 2B, first radiographic evaluation will occur at week 12 following the first dostarlimab dose and every 6 weeks (±10 days) thereafter, independent of cycle delays and/or dose interruptions. Radiographic evaluations and serum-based tumor marker testing may also be conducted as clinically indicated when progression of disease is suspected. The same radiographic modality (CT or MRI) should be used throughout the study for a given patient. Brain scans will be conducted if clinically indicated. Bone scans will be conducted per standard of care. After 1 year of radiographic

assessments, patients in Part 2A and Part 2B will have imaging and assessment of serum-based tumor markers performed every 12 weeks (84 ±10 days) until PD. If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, radiographic scans and appropriate testing of serum tumor markers should continue at the specified intervals (i.e., every 12 weeks after the first dostarlimab dose and every 6 weeks thereafter during the first year and every 12 weeks after 1 year of study treatment) until PD is confirmed or alternate anticancer therapy is started, whichever comes first. In Part 2B, all radiographic images/scans will be sent to a central imaging vendor upon acquisition and archived for future evaluation if needed.

Per irRECIST, patients who achieve complete response (CR) or partial response (PR) should have the response confirmed; tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (i.e., 6 weeks after the previous scan), whichever is clinically indicated. In addition, it is highly recommended that PD be confirmed a minimum of 4 weeks and up to 6 weeks after the first PD assessment (see 6.3.1.5 and Appendix B). Based on a recognized phenomenon[50] of transient tumor flare in the first few months after the start of immunotherapy with subsequent disease response, patients treated with dostarlimab will be permitted to continue treatment beyond initial irRECIST defined PD while awaiting confirmation of PD. To continue study treatment after initial evidence of PD, patients must be clinically stable (i.e., no signs or symptoms of clinically significant or rapid progression of disease, including worsening of laboratory values or decline in performance status; no progressive tumor at critical anatomical sites [e.g., cord compression, intracranial tumor hemorrhage, etc] requiring urgent medical intervention). It is highly recommended that clinically stable patients should not be discontinued until progression is confirmed (see Appendix B for irRECIST detailed guidance).

Serum samples for PK determination as well as antidrug antibody (ADA) assessment will be collected prior to, during, and after treatment with dostarlimab. The serum samples will be analyzed using enzyme-linked immunosorbent assay (ELISA) for dostarlimab PK analysis and electrochemiluminescence (ECL) for dostarlimab ADA analysis, respectively. Area under the concentration-time curves (AUCs) will be derived based on the results of serum PK sample analysis. Results of 3-tier ADA assays (screening, confirmation, and titer) and competitive ligand binding assay as neutralizing antibody assay (NAb) will be correlated with clinical activity, PK, and safety assessments.

During Part 1 and Part 2, blood cells may be assessed for PD-1 receptor occupancy prior to and after the first dose of dostarlimab (details for sample collection are provided in the Study Manual). In addition, these analyses may include, but are not limited to, assessing changes in serum cytokines to better characterize the clinical activity of dostarlimab and may be considered in the selection of the RP2D.

To better understand the effect of dostarlimab on the immune response and to potentially identify markers that are predictive and/or prognostic of drug activity, blood samples for biomarker analysis will be obtained pre-dose on Day 1 of each cycle up to and including Cycle 6 in both Part 1 and Part 2. Biomarkers will also be evaluated in archival and new tumor samples obtained from patients where available.

All patients will undergo an end-of-treatment (EOT) visit conducted 30 days (Q2W or Q3W schedules) or 42 days (Q6W schedule) (±7 days) after the last date of study drug administration

and a safety follow-up visit conducted 90 days (±7 days), after last date of study drug administration. After the 90-day safety follow up visit, patients will enter the post-treatment follow-up period for telephone assessment of survival status every 90 days (±14 days).

PRO assessments (EQ-5D-5L and EORTC QLQ-C30) will be collected during scheduled visits for all patients in Cohorts A1 and F enrolled under Amendment 3 and subsequent amendments, i.e. every 3 weeks ±7 days for the first 12 weeks, in alignment with study drug administration, and every 6 weeks (±7 days) thereafter, in alignment with tumor imaging assessments, while the patient is receiving study treatment. Once a patient discontinues treatment, PRO assessments will be performed during the end-of-treatment (EOT) visit, the safety follow-up visit, and during the post-treatment follow-up period every 90 days (±14 days).

All AEs and serious adverse events (SAEs) will be collected and recorded for each patient from the day of signing the ICF until 90 days after end of treatment visit (or until alternate anticancer therapy is initiated, whichever occurs first), and any pregnancies are to be reported through 150 days post-treatment. All AEs and SAEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

Independent Data Monitoring Committee

To ensure subjects' safety during Part 2B of the study, safety data will be reviewed by an Independent Data Monitoring Committee (IDMC) on an ongoing basis. Based on the available safety data, the IDMC will decide by consensus on continuation, modification, or suspension of the study or of a particular expansion cohort. The IDMC may modify the frequency of meetings as deemed appropriate during the course of the trial.

4. STUDY POPULATION

4.1. Inclusion Criteria

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Patient is at least 18 years of age.
2. Patient has proven recurrent or advanced solid tumor and has disease progression after treatment with available anti-cancer therapies, or is intolerant to treatment that meets the requirements for the part of the study they will participate in:
   a. Part 1: Any histologically or cytologically proven recurrent or advanced solid tumor.
   b. Part 2A: Any histologically or cytologically proven recurrent or advanced solid tumor
   c. Part 2B: Histologically of cytologically proven recurrent or advanced solid tumor with measurable lesion(s) per RECIST v.1.1 and meets one of the following disease types:
      The criteria below should be met for patients participating in:
      i. Cohort A1 (dMMR/MSI-H endometrial cancer) and
      ii. [redacted]

3. Part 2B: Patients must have archival tumor tissue available that is formalin-fixed and paraffin-embedded.
   - For patients who do not have archival tissue, a new biopsy must be performed to obtain a tissue sample prior to study treatment initiation. For patients without available archival tissue, the biopsy should be taken from the tumor lesions (either primary or metastatic) that have easy accessibility and low biopsy-associated risks and will exclude biopsies of the liver, brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach or bowel
4. Female patients must have a negative serum pregnancy test within 72 hours prior to the date of the first dose of study medication; unless they are of non-childbearing potential. Non-childbearing potential is defined as:
   a. ≥ 45 years of age and has not had menses for > 1 year
   b. Amenorrheic for < 2 years without a hysterectomy and oophorectomy and have a follicle- stimulating hormone (FSH) value in the postmenopausal range upon pre-study (screening) evaluation
   c. 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, MRI, or CT scan.. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must fulfill the criteria in Inclusion Criteria 5. Information must be captured appropriately within the site's source documents.
5. Female patients of childbearing potential (see above) must agree to use 1 highly effective form of contraception with their partners (see Section 5.6.3 for a list of acceptable contraception methods) starting with the screening visit through 150 days after the last dose of study therapy.
6. Patient has an ECOG performance status of ≤ 2 for Part 1 and ≤ 1 for Part 2.

7. Patient has adequate organ function, defined as:
   a. Absolute neutrophil count (ANC) ≥ 1,500/μL
   b. Platelets ≥ 100,000/μL
   c. Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L
   d. Serum creatinine ≤ 1.5× upper limit of normal (ULN) or calculated creatinine clearance ≥ 50 mL/min using Cockcroft-Gault equation for patients with creatinine levels > 1.5× institutional ULN
   e. Total bilirubin ≤ 1.5× ULN AND direct bilirubin ≤ 1× ULN
   f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5× ULN unless liver metastases are present, in which case they must be ≤ 5× ULN
   g. International normalized ratio (INR) or prothrombin time (PT) ≤1.5× ULN unless patient is receiving anticoagulant therapy as long as PT or partial thromboplastin (PTT) is within therapeutic range of intended use of anticoagulants. Activated partial thromboplastin time (aPTT) ≤1.5× ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

4.2. Exclusion Criteria (Criteria apply to Part 1, 2A, and 2B):

Patients will not be eligible for study entry if any of the following criteria are met:

1. Patient has received prior therapy with an anti-PD-1, anti-PD-1-ligand-1 (anti-PD-L1), or anti-PD-1 ligand-2 (anti-PD-L2) agent.
2. Patient has known uncontrolled central nervous system (CNS) metastases and/or carcinomatous meningitis. Note: Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are clinically stable off corticosteroids for at least 7 days prior to study treatment. Carcinomatous meningitis precludes a patient from study participation regardless of clinical stability. Patients with primary CNS tumors are eligible for Cohort F as long as they are neurologically stable in the absence of systemic corticosteroid use for at least 14 days prior to the first dose of study treatment.
3. Patient has a known additional malignancy that progressed or required active treatment within the last 2 years. Exceptions include basal cell carcinoma of the skin, SqCC of the skin that has undergone potentially curative therapy, or in situ cervical cancer.
4. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease or active infection requiring systemic therapy. Specific examples include, but are not limited to, active, non-infectious pneumonitis; uncontrolled ventricular arrhythmia; recent (within 90 days) myocardial infarction; uncontrolled major seizure disorder; unstable spinal cord compression; superior vena cava syndrome; or any psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study (including obtaining informed consent).

5. Patient is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study, starting with the screening visit through 150 days after the last dose of study treatment.
6. Patient has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
7. Patient has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
8. Patient has known active hepatitis B (e.g., hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (e.g., hepatitis C virus ribonucleic acid [HCV RNA] [qualitative] is detected).
9. Patient has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease-modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Use of inhaled steroids, local injection of steroids, and steroid eye drops are allowed.
10. Patient has a history of interstitial lung disease.
11. Patient has not recovered (i.e., to ≤ Grade 1 or to baseline) from radiation- and chemotherapy-induced AEs or received transfusion of blood products (including platelets or red blood cells) or administration of colony-stimulating factors (including granulocyte-colony stimulating factor [G-CSF], granulocyte macrophage colony-stimulating factor [GM-CSF] or recombinant erythropoietin) within 3 weeks prior to the first dose of study drug.
12. Patient has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks prior to the first dose of study drug.
13. Patient has received prior anti-cancer therapy (chemotherapy, targeted therapies, radiotherapy, or immunotherapy) within 21 days, or less than 5 times the half-life of the most recent therapy prior to study Day 1, whichever is shorter. Note: palliative radiation therapy to a small field > 1 week prior to Day 1 of study treatment may be allowed.
14. Patient has not recovered adequately (≤ Grade 1) from AEs and/or complications from any major surgery prior to starting therapy.
15. Patient has received a live vaccine within14 days of planned start of study therapy.
16. Patient has a known hypersensitivity to dostarlimab components or excipients.

4.3. Patient Withdrawal and Replacement

4.3.1. Discontinuation from Treatment:

Patients may be discontinued from study treatment at any time. Specific reasons for discontinuing treatment include the following:

- AE, including DLTs
- PD as outlined in Section 6.3 or based on clinical criteria by Investigator

- Risk to patients as judged by the Investigator and/or Sponsor
- Severe noncompliance with protocol as judged by the Investigator and/or Sponsor
- Patient request
- Patient becomes pregnant
- Withdrawal of consent by the patient, who is at any time free to discontinue participation in the study, without prejudice to further treatment
- Death

Patients who discontinue from study treatment will continue to receive follow-up assessments (see Table 3, Table 4, Table 5, and Table 6) as part of the study unless they are discontinued from the study (Section 4.3.2).

4.3.2. Discontinuation from the Study

Patients may be discontinued from the study for any of the following reasons:

- Withdrawal of consent by the patient, who is at any time free to discontinue participation in the study, without prejudice to further treatment
- Loss to follow-up
- Death
- Sponsor decision to terminate study

If a patient is thought to be lost to follow-up, discontinues study treatment, or discontinues the study, attempts should be made to contact the patient to determine the reason for discontinuation. For patients 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 patient before the patient is deemed lost to follow-up.

4.3.3. Replacement of Patients

After consultation between the Investigators and Sponsor, enrollment may be extended to replace patient(s) that become non-evaluable for safety during Part 1 and Part 2A.

In Part 2B, patients who discontinue prior to receiving the first dose of study medication will be replaced.

4.4. Patient Identification and Randomization

4.4.1. Patient Identification

All patients who enter into the screening period of the study (defined as the point at which the patient signs the ICF) will receive a unique patient identification number. This number will be used to identify the patient throughout the study and must be used on all study documentation related to that patient. A patient will be considered enrolled when the patient has been consented, screened, and all eligibility criteria have been confirmed in the electronic case report form (eCRF). The patient identification number must remain constant throughout the entire study; it must not be changed at the time of enrollment.

4.4.2. Randomization Scheme

Not applicable, as this is a single-arm study.

5. STUDY MEDICATION

5.1. Identity

Dostarlimab is an IgG4 antibody and will be supplied as a solution in vials containing 160 mg or 500 mg (20 mg/ml or 50 mg/ml, respectively, see Section 5.4).Administration

Dostarlimab will be administered using a 30 minute IV infusion (with a -5 minute and +15 minute window permitted). In Part 1, patients will receive dostarlimab every 2 weeks (Q2W) on Day 1 and Day 15 of each cycle; cycle length is 28 days. Patients enrolled specifically for additional PK/PDy sampling in Part 1 will not receive dostarlimab on Cycle 1/Day 15, but the rest of the treatment schedule will remain the same as DL cohorts.

For Part 1 weight-based dosing, the dose (mg/kg) to be administered will be based on the patient's weight within the 30 days prior to each treatment administration and will depend on cohort assignment and part of the study.

In Part 2A, patients will receive a fixed Q3W or Q6W dose on Day 1 of each cycle. Cycle duration for Q3W dosing is 21 days and Q6W dosing is 42 days.

In Part 2A, both fixed-dose schedules were determined to be safe, and the RP2D was determined to be 500 mg dostarlimab Q3W for the first 4 cycles followed by 1000 mg dostarlimab Q6W for all subsequent cycles until patients meet any criteria for discontinuation. This dosing schedule will be used in Part 2B.

Please refer to the Study Manual for details on the administration of dostarlimab.

5.1.1. Dose of Dostarlimab

5.1.1.1. Part 1 Dose Schedule

Part 1 (dose escalation) will initially evaluate 3 ascending weight-based dose levels (DLs) of dostarlimab, 1 mg/kg, 3 mg/kg and 10 mg/kg, administered via intravenous (IV) infusion using a modified 3+3 design (see Section 3.1.2 for details on dose escalation rules). Further dose escalation may be considered in additional cohort(s) at potential dose levels of 15 mg/kg or 20 mg/kg (not to exceed 20 mg/kg) following agreement between the Investigators and Sponsor.

5.1.1.2. Results from Part 1

In Part 1, dostarlimab was tested at 1mg/kg Q2W, 3mg/kg Q2W, and 10mg/kg Q2W dose levels using modified 3+3 design. No DLTs were observed. Based on PK/PDy data along with observed anti-tumor activity, it was decided that testing higher dose levels was not warranted. Therefore, 10mg/kg Q2W was the highest dose tested in Part 1, which also was found to be safe and well tolerated. MTD was not reached

5.1.1.3. Rationale for the fixed dose levels tested in Part 2

In the Part 1 dose escalation study eighteen patients received dostarlimab, administered as a 30 minute infusion. Six patients were dosed at 1 mg/kg, three patients at 3 mg/kg and nine patients at 10 mg/kg, respectively. dostarlimab exhibited dose proportional PK across all dose groups tested. The mean C_{max} was approximately 21, 66, and 224 µg/mL and the mean AUC was

approximately 3378, 10999, and 36770 h*µg/mL for dose levels 1, 3, and 10 mg/kg, respectively. The time of peak serum concentration ranged from 0.5-3 hours for all 3 treatment groups. The estimated terminal half-life was about 12 days.

A two-compartmental model best described the observed PK data and was used to predict the dose and regime. The effect of body weight on clearance of dostarlimab was also explored. Body weight over the range of 45.6 to 145.6 kg, was found not to be a significant covariate for clearance. Dose selection was guided primarily by the observed receptor occupancy data from peripheral blood cells. Full receptor occupancy was achieved at dostarlimab serum concentrations of 2.435 µg/mL and above. The model predicted C_{trough} at steady state for the 500 mg Q3W and 1000 mg Q6W are 51.1 and 29.2 µg/mL with 90% confidence interval of (13.4, 111.1) and (4.1, 78.5), respectively. The projected mean and 90% lower bound of C_{trough} at 500 mg Q3W and 1000 mg Q6W are about 21.0 and 12.0; 5.5 and 1.7 fold higher than the level required for full receptor occupancy of peripheral blood cells. Taken together, these data are highly supportive of the proposed flat dose of 500 mg for 4 cycles Q3W followed by 1000 mg Q6W for all subsequent cycles, to be further evaluated in the fixed-dose safety evaluation cohorts in Part 2A, to gain additional confidence around PK and safety of these dosing schedules.

5.1.1.4. Part 2 Dose Schedule

Part 2A (fixed-dose safety evaluation cohorts) evaluated safety and tolerability of 2 fixed-doses of dostarlimab administered Q3W or Q6W using 6+ 6 design (see Figure 1). Patients enrolled in Q3W and Q6W cohorts in Part 2A received 500 mg and 1000 mg fixed dostarlimab dose, respectively, via IV infusion on Day 1 of every cycle.

5.1.1.5. Results from Part 2

In Part 2A, no DLTs were observed, and both fixed doses tested were found to be safe. Based on these results, the RP2D was determined to be 500 mg dostarlimab Q3W for the first 4 cycles followed by 1000 mg dostarlimab Q6W for all subsequent cycles. This dosing schedule will be used in Part 2B.

5.2. Dose-Limiting Toxicity

The following are to be considered DLTs for this study (as assessed during 1st cycle of Part 1 and 2A):

- Any treatment-related Grade ≥ 3 non-hematologic clinical (non-laboratory) toxicity excluding:
  - Nausea and vomiting resolving to ≤ Grade 1 within 48 hours
  - Grade 3 diarrhea with duration < 48 hours
  - Grade 3 fatigue with duration < 7 days
  - Infusion-related reaction (see Table 2)
- Any treatment-related non-hematologic toxicity specifically defined as:
  - ≥ Grade 2 uveitis, eye pain, or blurred vision that does not resolve with topical therapy within 2 weeks

- ≥ Grade 2 immune-related endocrine toxicity that requires hormone replacement (except Grade 2 thyroiditis or thyroid dysfunction)
- ≥ Grade 2 colitis or diarrhea that persists for ≥ 7 days despite adequate steroid therapy
- Any toxicity that results in a treatment delay of ≥ 7

- Any treatment-related Grade ≥ 3 non-hematologic laboratory abnormality if:
  - Medical intervention is required to treat the patient, or
  - The abnormality leads to hospitalization, or
  - The abnormality persists for ≥ 7 days.
- Any treatment-related hematologic toxicity specifically defined as:
  - Grade 4 thrombocytopenia for ≥ 7 days, or Grade 3 or 4 associated with bleeding or requiring platelet transfusion;
  - Grade 4 neutropenia for ≥ 7 days, or Grade 3 or 4 associated with infection or febrile neutropenia;
  - Grade 4 anemia, or Grade 3 anemia requiring blood transfusion

Toxicities will be assessed according to CTCAE v4.03. If multiple toxicities occur, the presence of DLT will be graded based on the most severe toxicity observed. Patients participating in Part 1 and Part 2A must be assessed by the Investigator before Cycle 2/Day 1 dose administration to determine whether patients meet DLT criteria and to confirm continuation of study treatment. Patients who experience DLT will be permanently discontinued from treatment.

5.3. Dose Modification

5.3.1. General Rules

For patients in Part 1, intra-patient dose escalation to a dose that has been tested and shown to be safe during dose escalation may be permitted following agreement between the Investigator and Sponsor.

In Part 2A, if both Q3W and Q6W doses are declared safe, patients enrolled in the Q3W cohort are permitted to change to Q6W dose schedule after having received at least 4 cycles of dostarlimab doses.

Study treatment dosing delays are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 28 days of the scheduled dostarlimab infusion. If a delay is > 28 days, the patient should be placed back on study therapy only after discussion with the Sponsor. Reasons for treatment delays of > 3 days should be documented in the eCRF.

AEs (both non-serious and serious) associated with dostarlimab 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, dostarlimab must be withheld for drug-related Grade 3 toxicities but may be resumed upon recovery to Grade ≤ 1; dostarlimab will be permanently discontinued for any drug-related Grade 4 event. dostarlimab must be discontinued for some Grade 3 immunologic-mediated AEs as described in Table 1.

The specific AEs typically observed with anti-PD-1 antibodies [50,51] will be managed according to the guidelines summarized below.

5.3.2. Immune-related Adverse Events of Interest and Guidelines for Management

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

For all irAEs of interest listed in Table 1, dostarlimab should be held until patient is clinically and metabolically stable and AEs are resolved to grade 1or less. If systemic steroids are used as a part of irAE management, total dose of daily steroids should be equal or less than prednisone 10mg at the time of resuming dostarlimab.

Please refer to Table 1 for details on the management of dostarlimab dose delays and discontinuation for specific events.

The recent joint ASCO and NCCN guideline for diagnosis and management of immune related adverse events treated with immune checkpoint inhibitor therapy may be used as a supplement to Table 1.[52]

All treatment delays (including any missed doses) and discontinuations, and the reason for delays or discontinuation of dostarlimab should be recorded in the eCRF.

Table 1 Guidelines for Treatment of Immune-Related Adverse Events of Interest

Toxicity	Hold Treatment For Grade	Restarting Treatment/ discontinuation
Uveitis	2	Restart the treatment when toxicity resolves to Grade 0
Diarrhea/colitis	2-3	Restart dosing when toxicity resolves to Grade 0-1.
	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 0-1.
	3-4 (AST or ALT > 5 × ULN or total bilirubin > 3 × ULN)	Permanently discontinue (see exception below)[a].
Type 1 diabetes mellitus (TIDM) or hyperglycemia	3-4 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.

Table 1 Guidelines for Treatment of Immune-Related Adverse Events of Interest (Continued)

Toxicity	Hold Treatment For Grade	Restarting Treatment/ discontinuation
Hypophysitis	2-4	For Grade 2-3 hold until hormonal therapy results return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0-1. For recurrence or worsening of ≥ Grade 2 hypophysitis after steroid taper has been completed and is on adequate hormone replacement therapy, permanently discontinue. For Grade 4, permanently discontinue.
Adrenal insufficiency	2-3	Hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0-1. For recurrent or worsening ≥Grade 2 adrenal insufficiency while adequate hormonal replacement is continuing, permanently discontinue study drug.
	4	Permanently discontinue.
Hypo- and hyperthyroidism	3	Hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0-1.
	4	Permanently discontinue.
Infusion-related reaction	2[b]	Restart dosing when toxicity resolves to Grade 0-1.
	3-4	Permanently discontinue.
Pneumonitis	2	Restart dosing when toxicity resolves to Grade 0-1. If Grade 2 recurs, permanently discontinue.
	3-4	Permanently discontinue.
Rash	3	Restart dosing when toxicity resolves to Grade 0-1
	4	Permanently discontinue
Renal failure or nephritis	2	Restart dosing when toxicity resolves to Grade 0-1.
	3-4	Permanently discontinue.
Recurrence of AEs after resolution to ≤ Grade 1	3-4	Permanently discontinue.

Abbreviations: AE=adverse event(s); ALT=alanine aminotransferase, AST=aspartate aminotransferase, T1DM=type 1 diabetes mellitus; ULN=upper limit of normal.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by ≥50% relative to baseline and lasts for at least 1 week, then patient should be discontinued.

[b] Upon resolution within 1 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 patient should be premedicated for the next scheduled dose; refer to Section 5.6.4, Infusion-related Reaction Treatment Guidelines, for further management details (See Table 2).

5.4. Packaging, Labeling, and Storage

Dostarlimab for injection is supplied in vials containing either 160 mg at a concentration of 20 mg/mL or 500 mg at a concentration of 50 mg/mL. The 50 mg/mL concentration will be implemented after appropriate approval from competent health authorities.

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.

All study treatment supplies must be stored in accordance with the Study Manual instructions and package labeling. Until dispensed or administered to the patients, the study treatment will be stored in a securely locked area, accessible to authorized personnel only.

5.5. Drug Accountability

The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatments throughout the clinical study.

Details of maintaining drug accountability, including information on the accountability log, will be provided in the Study Manual.

All dispensation and accountability records will be available for Sponsor review. The study monitor will assume the responsibility to reconcile the study treatment accountability log. The pharmacist will dispense study treatment for each patient according to the protocol and Study Manual, if applicable.

5.6. Previous and Concomitant Medications

5.6.1. Recording of Previous and Concomitant Medications

At screening, patients will be asked what medications they have taken during the last 30 days. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking or have taken since the previous visit.

Any medication the patient takes during the study other than the study treatment, including herbal and other nontraditional remedies, is considered a concomitant medication. All concomitant medications must be recorded in the eCRF, including the following: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

5.6.2. Prohibited Medications

Known prior medications that exclude a patient from participating in the study are described in the exclusion criteria (Section 4.2).

Patients are prohibited from receiving the following therapies during the screening and treatment phase of this study:

- Systemic anticancer or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than dostarlimab
- Radiation therapy is prohibited within 3 weeks prior to study Day 1 and during study treatment.

Note: Palliative radiation therapy to a small field >1 week prior to Day 1 of study treatment may be allowed.

- Any surgery that involves tumor lesions

  Note: Administration of radiation therapy or surgery done that involves tumor lesions will be considered as PD at the time procedure is performed.

- Systemic glucocorticoids for any purpose other than to manage symptoms of suspected immune related adverse events.
- Note: Use of inhaled steroids, local injection of steroids, and steroid eye drops are allowed. If medically deemed necessary (e.g. acute asthma or COPD exacerbation), investigators are allowed to use their judgment to treat patients with systemic steroids. In such cases, systemic steroids should be stopped at least 24 hours prior to the next dose of dostarlimab.
- Live Vaccines within 14 days prior to the first dose of study treatment. Seasonal flu vaccines that do not contain live viruses are allowed.

5.6.3. Contraception

It is not known if dostarlimab may have adverse effects on a fetus in utero. However, blockade of PD-L1 signaling in murine models of allogeneic pregnancy can eliminate fetomaternal tolerance and cause spontaneous abortion as indicated by increase in embryo resorption and a reduction in litter size.[53] Therefore, non-pregnant, non-breastfeeding women may only be enrolled if they are willing to use 1 highly effective form of contraception (from the list below) or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥ 45 years of age and has not had menses for > 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study.

The following are considered highly effective forms of contraception: hormonal contraceptives that include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents), intrauterine device (IUD), vasectomized partner, and abstinence, if this is the established and preferred contraception for the patient.

Female patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and through 150 days after the last study treatment. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

5.6.4. Rescue Medications and Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator, including but not limited to the items outlined below. Prophylactic cytokines (e.g. G-CSF) should be administered according to current ASCO guidelines.[54]

Note: it may be necessary to perform additional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

The following text details specific guidance by type of AE.

- **Pneumonitis:**
  - Treat with systemic corticosteroids, oral for Grade 2 (e.g., 0.5-1 mg/kg/day of prednisone or equivalent) and IV for Grade 3-4 (e.g., 1 to 2 mg/kg/day of prednisone or equivalent).
  - Administer additional anti-inflammatory measures, as needed.
  - Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks.
  - If Grade 2 and no improvement or worsening over 2 weeks, treat as Grade 3-4.
  - Consider prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis:**

  Monitor carefully 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 patients 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 diarrhea/colitis that persists > 3 days, administer oral corticosteroids (e.g., 0.5-1.0 mg/kg/day of prednisone or equivalent). If symptoms persist or worsen with steroids, treat as Grade 3-4.
  - For Grade 3 or 4 diarrhea/colitis that persists > 3 days, treat with IV steroids (e.g., 1 to 2 mg/kg/day of prednisone or equivalent) followed by high-dose oral steroids.
  - Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks.
- **Type 1 diabetes mellitus or ≥ Grade 3 hyperglycemia:**
  - For type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria, insulin replacement therapy is required.
- **Hypophysitis:**
  - Treat with systemic corticosteroids, oral for Grade 2 (e.g., 0.5-1 mg/kg/day of prednisone or equivalent) and IV for Grade 3-4 (e.g., 1 to 2 mg/kg/day of prednisone or equivalent).
  - Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks.

    - Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Adrenal Insufficiency**
    - Start with hormone replacement therapy as necessary including glucocorticoid and mineralocorticoid.
    - Monitor patients in endocrinology clinic periodically during treatment, and as indicated based on clinical evaluation
- **Hyperthyroidism or Hypothyroidism:**

  Thyroid disorders have been reported with other PD-1 inhibitors occurring 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:
        - Consider non-selective beta-blockers (e.g., propranolol) as initial therapy.
    - Grade 3-4 hyperthyroidism
        - Treat with an initial dose of IV corticosteroids followed by oral corticosteroids (e.g., 0.5-1 mg/kg/day of prednisone or equivalent). Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
    - Grade 2-4 hypothyroidism
        - Thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
- **Hepatitis:**
    - Treat with systemic corticosteroids, oral for Grade 2 (initial dose of 1-2 mg/kg/day of prednisone or equivalent) and IV for Grade 3-4 (1-2 mg/kg/day of prednisone or equivalent)
    - Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks.
- **Renal Failure or Nephritis:**
    - Treat with systemic corticosteroids, oral for Grade 2 (initial dose of 0.5-1 mg/kg/day of prednisone or equivalent) and IV for Grade 3-4 (1-2 mg/kg/day of prednisone or equivalent).
    - Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks.
- **Management of Infusion-related Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

- Uveitis:
    - Symptomatic (any grade): Hold and consult ophthalmologist for treatment with corticosteroid eye drops. Restart dosing after resolution of symptoms.
    - Recurrent symptomatic uveitis or symptomatic uveitis unresponsive to corticosteroids: Permanently discontinue.

Table 2 shows treatment guidelines for patients who experience an infusion-related reaction associated with administration of dostarlimab.

Table 2 Infusion-related Reaction Treatment Guidelines

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 patient 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 hours	**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 patient is deemed medically stable in the opinion of the Investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment administration.**	Patient may be premedicated 1.5 hour (± 30 minutes) prior to infusion of dostarlimab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).

CTCAE Grade	Treatment	Premedication at Subsequent Dosing
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., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further study treatment administration.**	No subsequent dosing

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; NSAID=nonsteroidal anti-inflammatory drug; PO=by mouth.
Note: Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

6. ENDPOINTS AND METHODS OF ASSESSMENT

6.1. Safety Endpoints

Safety parameters evaluated during the conduct of the study include: treatment-emergent AEs (TEAEs), immune-related AEs of interest, clinical laboratory (hematology, chemistry, thyroid function, and urinalysis), vital signs, ECGs, physical examination, and use of concomitant medications.

6.1.1. Definitions

Adverse event: An *adverse event* is any untoward medical occurrence that occurs in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including clinically significant abnormal laboratory findings), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

A *treatment-emergent adverse event* is defined as any new AE that begins, or any preexisting condition that worsens in severity, after at least 1 dose of study treatment has been administered and throughout the treatment period until 90 days after end of treatment visit (or until the start of alternate anticancer therapy, whichever occurs earlier)

Serious adverse event: A *serious adverse event* is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
    - Note: This means that the patient is at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
    - Any AE that prolongs hospitalization will be considered an SAE.
    - Exception: Planned hospitalization (e.g., for observation, protocol compliance, elective procedures, social reasons, etc.) will not be considered an SAE; however, the reason for the planned hospitalization should be captured in medical history.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event(s)

An important medical event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or require intervention to prevent one of the above

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

Suspected Unexpected Serious Adverse Reaction (SUSAR): A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product set out in the Investigator's Brochure, Reference Safety Information section.

6.1.2. Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to the following categories.

6.1.2.1. Intensity

Investigators should assess the severity of AEs according to CTCAE. In general, CTCAE (v4.03) severity grades are:

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

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.)

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

A distinction should be made between **serious** and **severe** AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above in Section 6.1.1. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but may not be considered an SAE.

6.1.2.2. Causality

The Investigator will assess the causality/relationship between the study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions and all contributing factors:

- Related: A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment should be clinically plausible.

- Possibly related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals.
- Unlikely related: A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, or in which other drugs, chemicals or underlying disease provide likely explanations.
- Unrelated: A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors, or other drugs or chemicals).

6.1.3. Collecting and Recording Adverse Events

All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, ECG, reported by patient), must be documented in the eCRF.

All AEs and SAEs will be collected and recorded in the eCRF for each patient from the day of signed informed consent until 90 days after end of treatment visit (see Table 3, Table 4, Table 5, and Table 6 for schedules of events). All AEs and SAEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, any abnormal laboratory values have returned to baseline or normal levels, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

If an Investigator becomes aware of an SAE after the 90-day follow-up period after end of treatment visit and considers the SAE related to investigational product, the Investigator should report the SAE to the Sponsor according to timelines for reporting SAEs described in this section.

Adverse events may be volunteered spontaneously by the study patient, or discovered by the study staff during physical examinations or by asking an open, non-leading question such as: "How have you been feeling since you were last asked?" The Investigator will document the nature of AE, date of onset of the AE (and time, if known), date of outcome of the AE (and time, if known), severity of the AE, action taken with study drug as a result of the AE, assessment of the seriousness of the AE, and assessment of the causal relationship of the AE to study drug and/or study procedure.

Each AE should be recorded in the source and in the eCRF using the patient's own words (verbatim) unless, in the opinion of the Investigator, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual symptom.

Concomitant illnesses that existed before entry into the study will not be considered an AE unless the illness worsens during the treatment period. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page as well as on the SAE Report Form medical history section.

6.1.4. Reporting Disease Progression

The event of disease progression is an efficacy criterion and is therefore not considered an AE per se. Disease progression should be reported within the eCRF. If AEs/SAEs occur in relation to disease progression that are not consistent with the nature and natural progression of the patient's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements described in Section 6.1.2 and Section 6.1.6.

6.1.5. Reporting of Overdose

For weight based doses, an overdose of dostarlimab is defined as any dose that is ≥ 20% than the intended dostarlimab dose. For fixed doses, an overdose of dostarlimab is defined as any dose that is ≥20% than 1000mg Q6W.

All overdoses, regardless of associated AE/SAE are to be reported as described for SAEs and as per the SAE form completion guidelines.

6.1.6. Reporting Serious Adverse Events

6.1.6.1. Reporting of Serious Adverse Events

The Investigator must report all SAEs within 24 hours of becoming aware of the initial SAE or any follow-up information regarding the SAE using the SAE reporting contact information as printed on the SAE forms and in the SAE Completion guidelines.

For all SAEs, an SAE report form must be completed by the Investigator for all initial and follow-up SAEs. A follow-up SAE report must be completed each time an Investigator becomes aware of any additional information regarding the SAE. For the follow-up SAE Report Form, the following fields must be completed on each form: follow-up number, site number, patient/subject number, protocol number, and the SAE term(s) and date of awareness. Only the appropriate field(s) on the SAE Report Form where the Investigator received additional or updated information should be completed. Previously provided information does not have to be entered on the follow-up SAE Report Form.

Initial SAE reports and any additional supporting documentation (e.g., hospital reports, consultant reports, death certificates, autopsy reports, etc.) included with the SAE report should be sent to the Sponsor (or designee) within 24 hours of the Investigator/site awareness or receipt. If supporting documentation is provided, the Investigator should highlight all relevant and pertinent information. Also, any additional SAE documentation must be a clear photocopy with the patient's personal identifiers removed. The Investigator must sign and date all initial and final SAE forms.

The minimum information required for an initial SAE report is:

- Name of person sending the report (i.e., name, address of Investigator)
- Patient identification (screening/randomization number, initials [if permitted by local data privacy regulations], NOT patient name)
- Protocol number
- Description of SAE

- Causality assessment

In case the Investigator has no ability to either fax or email an SAE (e.g., due to technical issues), pharmacovigilance can be contacted by phone. If an SAE is reported via phone and during usual business hours, the Sponsor pharmacovigilance (or designee) will capture the information on a telephone contact form or similar method. Outside usual business hours, the message will be recorded and the required follow-up actions initiated during the next business day. Once technical issues are resolved, the Investigator should fax or email the completed SAE form to the Sponsor (or designee).

After receipt of the initial report, the Sponsor (or designee) will review the information and, if necessary, contact the Investigator to obtain further information.

6.1.6.2. Submission and Distribution of Serious Adverse Events

Per regulatory requirements, if an event is assessed by TESARO as a Serious Unexpected Suspected Adverse Reaction (SUSAR) it will be submitted to the Regulatory Authorities. In addition to this, a copy of the report (CIOMS or MedWatch 3500A) will be distributed to the Investigators/site and to the respective Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with US and EU Regulations and Directives, or as per national regulatory requirements in participating countries.

TESARO has delegated the reporting of SUSARs to Regulatory Health Authorities ex-US to a third party. Information about the third parties responsible for SUSAR reporting to Health Authorities, investigators, IRBs and IECs, is listed in the clinical trial application form.

6.1.7. Pregnancy

Pregnancies occurring in patients enrolled in this study must be reported and followed to outcome. If a female patient inadvertently becomes pregnant while on study treatment, the patient will immediately be removed from the study. Any pregnancies that occur within 150 days following the last dose of study treatment must be reported in the eCRF.

Pregnancy alone is not regarded as an AE unless there is a possibility that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Pregnancy is not considered an SAE unless there is an associated serious outcome. Spontaneous abortions should always be reported as SAEs.

Any SAE that occurs during pregnancy must be recorded on the SAE Report Form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

The Investigator should complete the Initial Pregnancy Notification report form and forward it to the Sponsor (or designee) within 24 hours of knowledge of the pregnancy. If there is an associated serious outcome, then both the Initial Pregnancy Notification report form and SAE report form should be completed.

The Investigator should follow-up with the patient until delivery or termination of pregnancy even if the patient was withdrawn from the clinical study or if the clinical study has finished. At that time, the Pregnancy Outcome report form should be completed and submitted to the Sponsor within 24 hours after the Investigator becomes aware of the pregnancy outcome.

In the event the pregnancy outcome occurs following the end of the study and database lock, the Investigator will report the pregnancy outcome to the Sponsor (or designee) within 24 hours after the outcome of the pregnancy is known to the Investigator in accordance with the procedure for reporting SAEs (see Section 6.1.6).

6.1.8. Clinical Laboratory Assessments

The following laboratory variables will be determined in accordance with the schedule of events (Table 3, Table 4, Table 5, Table 6). These tests will be performed by the local laboratory at the clinical site.

- **Complete blood count:**
  - Hemoglobin
  - Mean corpuscular volume
  - White blood cell count
  - Platelets
  - Mean platelet volume (optional)*
  - Differential white cell count

  * Note: Although mean platelet volume collection is optional, it is highly encouraged, especially for patients with high-grade thrombocytopenia.
- **Coagulation factors:**
  - INR
  - aPTT
- **Serum chemistry:**
  - Sodium
  - Potassium
  - Calcium
  - Magnesium
  - Chloride
  - Glucose
  - Creatinine and estimated creatinine clearance using Cockcroft-Gault formula (see Appendix D)
  - Urea or blood urea nitrogen
  - Amylase
  - Bilirubin (total and direct)
  - Alkaline phosphatase
  - AST
  - ALT
  - Total protein
  - Albumin
  - Lactate dehydrogenase
- **Urinalysis:**
  - Specific gravity
  - Leukocyte esterase
  - Nitrite
  - Blood
  - Protein
  - Glucose
  - Ketones
  - Microscopy (if clinically indicated)
- **Thyroid panel** (i.e., TSH, T3 or FT3, FT4, or equivalent tests),
- **Serum pregnancy testing / urine pregnancy testing**

- **Hepatitis B surface antigen (HBsAg) and hepatitis C virus ribonucleic acid (HCV RNA) testing (only when medically indicated based on history and physical examination)**

Any laboratory values assessed as clinically significant should be recorded as an AE. When determining the clinical significance of any ≥ grade 3 laboratory abnormalities (hematological and non-hematological AEs), CTCAE guidelines have to be considered. Any ≥ grade 3 laboratory abnormality that require treatment or hospitalization should be reported as an AE. If SAE criteria are met, the event should be recorded and reported according to the SAE reporting process (see Section 6.1.6).

6.1.9. Physical Examination and Vital Signs

Physical examinations, including height (screening only), weight, and vital signs (blood pressure [BP], pulse, and temperature), will be performed in accordance with the schedule of events (Table 3, Table 4, Table 5, and Table 6).

Any physical examination or vital signs assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met, the event should be recorded and reported according to the SAE reporting process (see Section 6.1.6).

6.1.10. Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG scale (see Appendix C) in accordance with the schedule of events (Tables 3-6). The same observer should assess performance status each time.

6.1.11. Additional Safety Assessments

All patients will undergo ECGs in accordance with the schedule of events (Tables 3-6). Electrocardiograms should be performed prior to any blood draws. Patients will be supine or in a semi-recumbent position (about 30 degrees of elevation) and rested for approximately 2 minutes before ECGs are recorded.

Any ECG findings assessed as clinically significant should be recorded as an AE. If SAE criteria are met, the event should be recorded and reported according to the SAE reporting process (see Section 6.1.6).

6.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics consist of those variables that are assessed at Screening/Baseline.

6.2.1. Patient Eligibility

Compliance with inclusion and exclusion criteria will be assessed as outlined in Section 4.1 and Section 4.2.

6.2.2. Patient Demography

Patient demography consists of age at screening, race, ethnicity, and sex.

6.2.3. Disease History

For disease history the following will be documented:

- Date of first diagnosis
- Tumor type
- Stage at time of initial diagnosis and study entry
- Histology and grade of disease at diagnosis and most recent biopsy if additional biopsy performed
- Information on prior anticancer treatment:
  - Intent (adjuvant, neoadjuvant, curative, palliative)
  - Date of start of prior treatment
  - Agents used in prior treatment
  - Date of last dose of prior treatment
  - Best response for each prior anticancer treatment
  - Date of recurrence for each prior anticancer treatment
- Information on previous radiation therapy
- Information on previous anti-cancer surgeries

6.2.4. Medical and Surgical History

Major medical and surgical history (including medication history) will be collected. Details of any prior invasive malignancy will be collected. Medical and surgical history will be obtained by interviewing the patient or by reviewing the patient's medical records.

6.2.5. Previous and Concomitant Medications

Previous and concomitant medication will be documented as described in Section 5.6. Medications will be coded using World Health Organization Anatomical Therapeutic Chemical classification.

6.3. Clinical Activity Endpoints

6.3.1. Evaluation of Tumor Response

6.3.1.1. Overview

The clinical activity of treatment with dostarlimab will be evaluated by assessment of tumor response to treatment according to RECIST v1.1[55] (Appendix A) and irRECIST[56] (6.3.1.4 and Appendix B). Serum-based tumor marker data (e.g., CA-125 for OC) will not be used for defining objective responses or PD; however, these can be used for clinical decisions.

Investigators will use irRECIST-based assessment to make clinical decisions. In Part 2B, all radiographic images/scans at the time points specified in Table 6, as well as any unscheduled

images/scans, will be sent by the study sites to the central imaging vendor upon acquisition and archived for potential future evaluation.

The process for image collection and transmission to the central imaging vendor can be found in the Study Manual.

Tumor imaging (chest, abdomen, and pelvis [plus brain if clinically indicated]) should be performed by CT (preferred). MRI should only be used when CT is contraindicated or for imaging of the brain, but the same imaging technique should be used in a patient throughout the study. CT scan is the more commonly used modality and is preferred for the majority of patients. An MRI can be utilized if clinically appropriate. Positron emission tomography (PET)/CT may be used according to RECIST guidelines.

If brain CT/MRI is clear at screening, repeat imaging is not required in the absence of clinical indication requiring follow-up.

Bone scans should be conducted per standard of care.

6.3.1.2. Timing of Radiographic Evaluations

Part 1

All patients will undergo serial radiographic assessments to assess tumor response. Initial tumor imaging at screening must be performed within 21 days prior to the date of the first dose of study treatment. Scans performed prior to the signing of the ICF as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within 21 days prior to first dose date.

The first on-study imaging assessment should be performed at 10 weeks (70 ±10 days) from the date of first dose of study treatment. Subsequent tumor imaging should be performed every 10 weeks (70 ±10 days) or more frequently if clinically indicated and at the time of suspected disease progression. After 1 year of radiographic assessments, patients will have imaging performed every 12 weeks (84 ±10 days). Imaging should not be delayed for delays in cycle starts.

Per irRECIST (see Appendix B), irCR or irPR should be confirmed by a repeat tumor imaging assessment. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (i.e., 10 weeks after the previous scan), whichever is clinically indicated. irPD should be confirmed a minimum of 4 weeks and up to 10 weeks after the first PD assessment; patients may remain on study treatment while awaiting confirmation provided the patient is clinically stable (see 6.3.1.5).

Continue to perform imaging until whichever of the following occurs:

- Confirmed irPD per irRECIST
- The start of new anticancer treatment
- Withdrawal of consent
- Death
- Lost to follow up
- End of the study (last visit, last patient)

Part 2

All patients will undergo serial radiographic assessments to assess tumor response. Initial tumor imaging at screening must be performed within 28 days prior to the date of the first dose of study treatment. Scans performed prior to the signing of the ICF as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within 28 days prior to first dose date.

The first on-study imaging assessment should be performed at 12 weeks (84 ±10 days) from the date of first dose of study treatment. Subsequent tumor imaging should be performed every 6 weeks (42 ±10 days) or more frequently if clinically indicated, and at the time of suspected PD. After 1 year of radiographic assessments, patients will have imaging performed every 12 weeks (84 ±10 days). Imaging should not be delayed for any dose or cycle interruptions.

According to irRECIST (see Appendix B), irCR or irPR should be confirmed by a repeat tumor imaging assessment. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated. If new response (ie, irCR or irPR) is seen after 1 year, a confirmatory scan should be conducted between 4-6 weeks after the new response was first observed. It is highly recommended that irPD should be confirmed a minimum of 4 weeks and up to 6 weeks after the first PD assessment; patients may remain on study treatment while awaiting confirmation provided the patient is clinically stable (see Section 6.3.1.5).

All patients including patients who discontinue study treatment for reasons other than PD must continue to perform imaging until at least one of the following occur:

- Confirmed irPD per irRECIST
- The start of new anticancer treatment
- Withdrawal of consent
- Death
- Lost to follow up
- End of the study (last visit, last patient)

6.3.1.3. Assessment of Response by RECIST v1.1

RECIST v1.1 will be used as the primary measure of tumor response for Cohorts A1, A2, and F by independent blinded central reviewers. Note that irRECIST will be followed in cases of PD to assess continuation of treatment in clinically stable patients until progression is confirmed (see Section 6.3.1.5).

Details on RECIST v1.1, including evaluation of target and non-target lesions and definitions of response are provided in Appendix A.

6.3.1.4. Assessment of Response by Immune-Related RECIST

RECIST v1.1 will be adapted to account for the unique tumor response characteristics seen during treatment with PD-1 inhibitors, such as dostarlimab.[56]

irRECIST will be used by local site Investigators to assess tumor response and progression and make treatment decisions.

According to irRECIST, after initial radiologic evidence of PD is seen, investigators can decide to continue to treat patients with dostarlimab until repeat imaging is available in 4-6 weeks, as long as patients are clinically stable (see also Section 6.3.1.5). Based on the findings on repeat imaging, the guidelines below should be followed. (see also Appendix B).

- If repeat imaging shows < 20% increase in tumor burden compared with nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), treatment may be continued/resumed, and the next tumor imaging should be conducted according to the protocol schedule (every 6 weeks following an initial imaging study conducted 12 weeks after the first dostarlimab dose administration, or every 12 weeks if on study treatment for > 1 year).
- If repeat imaging confirms PD due to any of the scenarios listed below, patients will be discontinued from study therapy. Following confirmation of PD, if the Investigator believes there is clinical benefit, clinically stable patients without major safety issues may remain on treatment following discussion with the Medical Monitor.

  In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site Investigator should consider all target and non-target lesions, as well as any incremental new lesion(s).

  If ANY of the following occur by irRECIST on repeat imaging, PD is confirmed:

  - Tumor burden remains ≥ 20% and at least 5-mm absolute increase compared with nadir
  - Non-target disease resulting in initial PD is worse (qualitative)
  - New lesion resulting in initial PD is worse (qualitative)
  - Additional new lesion(s) since last evaluation
  - Additional new non-target progression since last evaluation

6.3.1.5. Treatment and Assessment After Progression

There is accumulating evidence indicating clinical benefit in a subset of patients treated with immunotherapy despite initial evidence of PD.[56] During study treatment, a patient with initial evidence of radiological PD may continue on study treatment until repeat imaging is obtained (at least 4 weeks and up to 6 weeks later, see Appendix B). Investigator's decision to continue treatment beyond the initial assessment of progression should be based on the patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. A patient may receive dostarlimab treatment while waiting for confirmatory imaging if he/she is clinically stable per following criteria:

- Absence of signs and symptoms indicating clinically significant progression of disease, including worsening of laboratory parameters
- No decline in performance status
- Does not have rapid progression of disease
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of PD (e.g., CNS metastases, cord compression)

Whenever possible, patients should not be discontinued until progression is confirmed. Following confirmation of PD, if the Investigator believes there is clinical benefit, clinically stable patients without major safety issues may remain on treatment following discussion with the Medical Monitor.

6.3.2. Efficacy Endpoints

6.3.2.1. Objective Response Rate

The primary efficacy endpoint is ORR, defined as the proportion of patients achieving CR or PR per RECIST v1.1 (Appendix A) for dMMR/MSI-H (Cohorts A1 [redacted]. Tumor assessments after the initiation of further anti-cancer therapy are excluded for the assessment of best overall response.

ORR based on independent blinded central review using RECIST v1.1 for Cohorts A1 [redacted] will be evaluated as a secondary endpoint.

irORR by irRECIST (Section 6.3.1.4 and Appendix B) for Cohorts A1, [redacted] will also be evaluated as a secondary endpoint.

6.3.2.2. Duration of Response

Duration of response (DOR) will be evaluated as a primary efficacy endpoint for dMMR/MSI-H (Cohorts A1 and F) or [redacted] patients, and is defined as the time from first documentation of CR or PR by RECIST v1.1 until the time of first documentation of PD evaluated using RECIST v1.1 based on independent blinded central review, or death due to any cause (Appendix A).

DOR based on independent blinded central review using RECIST v1.1 for Cohorts A1 [redacted] will be evaluated as a secondary endpoint.

6.3.2.3. Disease Control Rate

Disease control rate will be assessed for Cohorts A1, [redacted] as a secondary endpoint and is defined as the proportion of patients achieving CR, PR, or stable disease (SD) as assessed per RECIST v1.1. (Appendix A). Immune-related disease control rate will be assessed as a secondary endpoint for all cohorts in Part 2B and is defined as the proportion of patients achieving CR, PR, or SD as assessed per irRECIST.

6.3.2.4. Immune-Related Duration of Response

Immune-related duration of response will be evaluated as a secondary endpoint for all cohorts in Part 2B and is defined as the time from first documentation of CR or PR by irRECIST until the time of first documentation of PD (subsequently confirmed) per irRECIST (Appendix A)

6.3.2.5. Progression-Free Survival

Progression-free survival will be assessed as a secondary endpoint and is defined as the time from date of first dose to the earlier date of assessment of progression or death by any cause in the absence of progression based on: (1) the time of first documentation of PD per RECIST v1.1 (for cohorts A1, [redacted]; and (2) the time of first documentation of PD (subsequently confirmed) per irRECIST for all cohorts in Part 2B (Section 6.3.1.4 and Appendix B).

6.3.2.6. Overall Survival

OS will be assessed as a secondary endpoint and is defined as the time from date of first dose of study treatment to the date of death by any cause.

6.3.2.7. Patient-Reported Outcomes

Cancer-specific health-related quality of life (HRQoL) will be assessed using two PRO instruments: the EQ-5D-5L and the EORTC QLQ-C30. TheEQ-5D-5L, a non-disease specific HRQoL questionnaire, is an update of the EQ-5D-3L instrument, one of the most widely used instruments to measure HRQoL across oncology and non-oncology indications. It consists of 2 pages – the EQ-5D-5L descriptive system and the EQ Visual Analogue scale (EQ VAS). The descriptive system comprises the same 5 dimensions as the EQ-5D-3L (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). However, each dimension now has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as a cardinal score (EQ-5D-5L User Guide v2.0, October 2013).

In addition, the EORTC QLQ-C30 will be collected. The EORTC QLQ-C30 is a 30-item questionnaire used to measure HRQoL in patients with cancer. The EORTC QLQ-C30 is composed of both multi-item scales and single item measures. These include five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea/vomiting, and pain), a global health status/quality of life (QOL) scale, and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Each of the multi-item scales includes a different set of items – no item occurs in more than one scale. The QLQ-C30 employs a week recall period for all items and a 4-point scale for the functional and symptom scales/items with response categories "Not at all," "A little," "Quite a bit" and "Very much." The two items assessing global health status/QOL utilize a 7-point scale ranging from 1 ("Very Poor") to 7 ("Excellent").[57]

PROs will be assessed as an exploratory endpoint for patients in Cohorts A1 and F enrolled under Amendment 3 and subsequent amendments.

6.4. Pharmacokinetics and Antidrug Antibodies

Complete instructions for collection, processing, shipping, and handling of samples for PK and ADA analysis are detailed in the Study Manual.

6.4.1. Pharmacokinetic Analysis

Blood samples for determination of serum levels of dostarlimab will be collected from patients in both Part 1 and Part 2. Overviews of sampling times for blood for PK analysis are provided in Table 7, Table 8, Table 9, and Table 10. All sampling times are relative to the start of the dostarlimab infusion.

PK parameters of interest that will be derived are AUC from time 0 to last assessment ($AUC_{0\text{-last}}$), AUC from time 0 to infinity ($AUC_{0\text{-}\infty}$), minimum concentration (C_{min}), maximum concentration (C_{max}), clearance (CL), volume of distribution (V_z), AUC at steady state (AUC_{ss}), C_{min} at steady state ($C_{min,ss}$), and C_{max} at steady state ($C_{max,ss}$).

6.4.2. Analysis for Antidrug Antibodies

Serum samples for the determination of anti-dostarlimab antibodies will be the same samples collected as for PK (Table 7 through Table 10). Minimally, ADA will be analyzed using electrochemiluminescence (ECL) with predose and at/after 96 hr postdose samples from all cycles collected. Additional samples for ADA determination will be collected upon treatment discontinuation at a safety follow-up visit (i.e., approximately 90 days after the last dose of dostarlimab).

6.5. Pharmacodynamics

During Part 1, blood cells may be assessed for PD-1 receptor occupancy in Cycle 1 on Days 1, 3, 15 in all patients; in additional patients enrolled to better characterize the PK/PDy profile that do not receive a dose on C1D15, blood cells may be assessed on Day 22 and on Cycle 2/Day 1. In addition, these analyses may include, but are not limited to, assessing changes in serum cytokines to better characterize the clinical activity of dostarlimab and may be considered for selection of the RP2D.

During Part 2A, blood cells may be assessed for PD-1 receptor occupancy on days 1, 5, 15, and 22 in the Q3W cohort, and on study days 1, 5, 15, 29, and 43 in the Q6W cohort.

In Part 2B, predose blood samples collected on Day 1 of Cycle 1 and 2 and upon progression may be assessed for PD-1 receptor occupancy. This sample will not be collected from patients enrolled under Amendment 4 and subsequent amendments.

6.6. Biomarkers

To better understand the effect of dostarlimab on the immune response and to potentially identify markers that are predictive and/or prognostic of drug activity, blood samples for biomarker analysis will be obtained pre-dose on Day 1 of each cycle up to and including Cycle 6 in both Part 1, Part 2A, and Part 2B. Blood based biomarkers may include serum cytokines, gene expression of circulating immune cells, circulating tumor DNA, and circulating tumor cells.

Biomarker classifiers will also be evaluated in archival and new tumor samples obtained from patients where available. In the subset of patients who undergo serial biopsies, biomarkers will be evaluated in new tumor samples obtained at baseline, approximately 4-6 weeks after initiating study treatment and, whenever possible, at the time of PD. Tumor based biomarkers may include description of immune cells, gene expression profiling for immune-related and tumor-related proteins, and assessment of tumor genome for mutations and/or alterations (e.g., MMR/MSI and POLE mutations).

In addition to monitoring immune responses, tumor genomic alterations (e.g., MMR/MSI and POLE) may be correlated with other immune-related biomarkers and with clinical activity in Part 2B.

7. STUDY CONDUCT

7.1. Schedule of Procedures

The schedules of events are provided in Table 3 (Part 1) and Table 4 (Part 2A Q3W), Table 5 (Part 2A Q6W), and Table 6 (Part 2 B). Table 7 (Part 1), Table 8 (Part 2A Q3W), Table 9 (Part 2A Q6W), and Table 10 (Part 2B) present the PK/PDy sampling schedules.

Table 3: Part 1 Schedule of Events: Part 1

Cycle/Visit:	Screening	Cycle 1[a]							Subsequent Cycles[a]		EOT[b]	Safety FUP[c]	FUP Assessments (every 90 ± 14 days) via telephone
Day: Procedure:	-21 to -1	1	2	3	5 (±24 hrs)	8 (±24 hrs)	15	22	Cycle n, Day 1	Cycle n, Day 15	30 ± 7 days	90 ± 7 days	
Informed consent[d]	X												
Inclusion/exclusion criteria review	X	X											
Demographics	X												
Medical, surgical, cancer, and medication history	X												
Blood sample for PK[e]		X	X	X	X	X	X	X	X	X		X	
Blood sample for PDy marker		X[f]		X			X	X[g]	X[f g]				
Blood sample for immunogenicity (ADA)[h]		X[f]	X	X	X	X	X	X	X	X		X	
Blood sample for exploratory biomarkers		X[f]							X[f i]				
Tumor Biopsy[j]	X								X		X		
Tumor assessment (RECIST and irRECIST)	X[k l]								X[k]		X[k]	X[k]	
Laboratory assessments:													
CBC w/differential	X[l]	X[m v]	X	X	X	X	X	X	X[v]		X	X	
Serum chemistry	X[l]	X[m v]	X				X		X[v]		X	X	
Coagulation	X[l]								X[n]				
Pregnancy test	X[l o]	X[m v]							X[o]		X[o]	X[o]	
HBV/HCV test[p]	X[l]												
Serum-based tumor markers (e.g., CA-125)	X[l]	X[m]							X[k]		X		
Urinalysis	X[l]	X							X		X	X	
Thyroid panel	X[l]								X[q]		X		
ECG	X[l r]	X[r]							X[r]		X[r]		
Physical examination	X[l]										X	X	
Symptom-directed PE		X	X	X	X		X		X	X			
Vital signs, height, and	X[l]	X	X	X	X	X	X	X	X	X	X		

Cycle/Visit:	Screening	Cycle 1[a]							Subsequent Cycles[a]		EOT[b]	Safety FUP[c]	FUP Assessments (every 90 ± 14 days) via telephone
Day: Procedure:	-21 to -1	1	2	3	5 (±24 hrs)	8 (±24 hrs)	15	22	Cycle n, Day 1	Cycle n, Day 15	30 ± 7 days	90 ± 7 days	
weight[s]													
ECOG performance status	X								X	X	X		
Concomitant medications	X												
AE monitoring	X[t]												
Dostarlimab (TSR-042) administered[u]		X					X[g]		X	X			
Survival assessment													X

Abbreviations: ADA=antidrug antibody; AE=adverse event; CBC=complete blood count; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End-of-treatment; FUP=follow-up; hr=hour(s); HBV=hepatitis B virus; HCV=hepatitis C virus; ICF=informed consent form; irRECIST=immune-related RECIST; IV=intravenous; MRI=magnetic resonance imaging; OC=ovarian cancer; PDy=pharmacodynamics; PE=physical examination; PK=pharmacokinetics; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event.

[a] Treatment cycles are 28 ± 3 days in duration, with the exception of Cycle 1, which is 28 ± 1 day, to accommodate PK sampling; see Table 7

[b] EOT visit should be completed 30 (±7) days after last study drug dose. Patients with ongoing AEs will be followed until resolution or stabilization of the AE.

[c] Safety follow-up visit should be conducted 90 (±7) days after last study drug dose or until initiation of new anticancer therapy, whichever comes first. Patients with ongoing AEs will be followed until resolution or stabilization of the AE.

[d] The ICF may be signed prior to the 21-day screening period.

[e] See Table 7 for the detailed schedule.

[f] Sample to be obtained prior to the dose of dostarlimab.

[g] Patients enrolled to better characterize the PK/PDy profile at any DL with DLTs observed in <33% of patients will not be administered dostarlimab on C1D15 and only these patients will have PDy analysis on C1D22 and pre-dose C2D1 (see Section 3.1.2).

[h] Serum samples for the determination of anti-dostarlimab antibodies will be the same samples collected as for PK (see Table 7 for detailed schedule).

[i] Up to and including Cycle 6 only.

[j] For patients who consent to optional serial biopsies, the biopsies will be obtained prior to initiation of study treatment, approximately 8 to 12 weeks after initiating study treatment and, whenever possible, at the time of PD (note: while the biopsy is voluntary, it is highly encouraged). A core biopsy is recommended (details are provided in the Study Manual); if an excisional or incisional biopsy is to be performed, it must be conducted on a non-target lesion. If a patient has had a biopsy prior to entering screening and within 12 weeks of study treatment, that biopsy may be accepted as the screening biopsy.

[k] Tumor assessment per RECIST and irRECIST via CT or MRI (chest, abdomen, and pelvis) required at screening, every 10 weeks (70 ±10 days)while on study treatment independent of cycle delays and/or dose interruptions, and/or at any time when progression of disease is suspected (A final set of radiographic images is required at the time of PD, if not done within the last 4 weeks). Appropriate testing of serum-based tumor markers (e.g., CA-125 for OC patients) should also be conducted in concordance with scans (i.e., every 10 weeks [70 ±10 days]) as clinically indicated. Brain scan will be conducted if clinically indicated; bone scans will be conducted per standard of care. After 1 year, patients who remain on treatment will have imaging performed every 12 weeks (84 ±10 days). If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, scans and appropriate serum-based tumor marker testing (e.g. CA-125 for OC patients) should continue at the specified intervals. Per RECIST v1.1, complete response (CR) or partial response (PR) should be confirmed; tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the

next scheduled scan (i.e., 6 weeks after the previous scan), whichever is clinically indicated. In addition, PD should be confirmed a minimum of 4 weeks and up to 6 weeks after the first PD assessment. Clinically stable patients should not be discontinued until progression is confirmed (see Section 6.3.1.5 and Appendix B).

[l] Standard of care tests/procedures, scans, laboratory assessments, ECGs, physical examinations, vital signs, height, and weight performed prior to the patient signing the ICF can be used as part of the screening assessments as long as the tests/procedures meet the protocol-required timelines (i.e., within 21 days of first dose for these procedures with the exception of the pregnancy test, which must be conducted within 72 hours of first dose date) and any relevant guidelines (e.g. diagnostic quality for scans).

[m] If screening laboratory testing (CBC, serum chemistry, serum-based tumor markers) performed within 72 hours prior to the date of first dose of study treatment on Day 1, repeat testing is not required

[n] To be conducted per standard of care for patients on anticoagulant therapy.

[o] Negative serum pregnancy test required within 72 hours prior to date of first dose of study treatment on Day 1 for females of childbearing potential; urine pregnancy test conducted every 3 months for duration of study (i.e., Cycle 4, Cycle 7, etc),at the 30-day EOT visit, and at the 90 day Safety FUP visit.

[p] If clinically indicated (e.g., history of intravenous drug use).

[q] Blood samples for thyroid panel (i.e., TSH, T3 or FT3, and FT4 or equivalent tests, where applicable) are to be collected every 6 weeks (42 ± 7 days) after Cycle 1/Day 1.

[r] Patients will undergo ECG monitoring at screening, Day 1 of each cycle, at EOT visit, and if clinically indicated.

[s] Vital signs include blood pressure, pulse, and temperature. Height obtained at screening only. Weight is obtained once every cycle on Day 1; Day 15 visits record only vital signs. For weight-based dosing, the dose (mg/kg) to be administered will be based on the patient's weight within the last 30 days prior to each treatment administration.

[t] AEs and SAEs are required to be captured through 90 days after cessation of study treatment (or until the start of alternate anticancer therapy, whichever occurs first), and any pregnancies that occur within 150 days post-treatment are to be captured.

[u] Administer dostarlimab on Cycle 1 Day 1 and then on Day 1 and Day 15 of all subsequent cycles. dostarlimab may be administered up to 3 days before or after the scheduled Day 1 of each cycle after Cycle 2, but not before the visit-required assessments. For weight-based dosing, the dose (mg/kg) to be administered will be based on the patient's weight within the last 30 days prior to each treatment administration.

[v] Samples can be collected up to 72 hours prior to dostarlimab administration.

Table 4: Part 2A Schedule of Events: Q3W Fixed-Dose Safety Evaluation Cohort

Cycle/Visit:	Screening	Cycle 1[a]	Cycle 2[a]	Cycle 3[a]	Cycle 4[a]	Cycle 5[a]	Cycle 6[a]	Cycle 7[a]	Cycle 8[a]	Cycle 9[a]	Cycle 10[a]	Cycle n[a]	EOT[b]	Safety FUP[c]	FUP Assessments[d] (every 90± 14 days) via telephone
Day: Day: Procedure:	-35 to -1	1	1	1	1	1	1	1	1	1	1	1	30 ± 7 days	90 ± 7 days	
Informed consent[e]	X														
Inclusion/exclusion criteria review	X	X													
Demographics	X														
Medical, surgical, cancer, and medication history	X														
Blood sample for PK/ADA[f]		X[f]	X[f]	X[f]	X[f]	X[f]	X[f]			X[f]		X[f]		X[f]	
Blood sample for PDy[f]		X[f]	X[f]												
Blood sample for Exploratory biomarkers[f]		X[f]	X[f]	X[f]	X[f]	X[f]	X[f]						X[f]		
Optional Tumor Biopsy[g]	X			X									X		
Tumor assessment (irRECIST)[h]	X[i]					X			X			X[h]	X	X	
Laboratory assessments:															

Table 4: Part 2A Schedule of Events: Q3W Fixed-Dose Safety Evaluation Cohort (Continued)

Cycle/Visit:	Screening	Cycle 1[a]	Cycle 2[a]	Cycle 3[a]	Cycle 4[a]	Cycle 5[a]	Cycle 6[a]	Cycle 7[a]	Cycle 8[a]	Cycle 9[a]	Cycle 10[a]	Cycle n[a]	EOT[b]	Safety FUP[c]	FUP Assessments[d] (every 90± 14 days) via telephone
Day: Day: Procedure:	-35 to -1	1	1	1	1	1	1	1	1	1	1	1	30 ± 7 days	90 ± 7 days	
CBC w/differential	X[i]	X[j k]	X[k l]	X[k l]	X[k l]	X[k l]	X[k l]	X[k l]	X[k l]	X[k l]	X[k l]	X[k l]	X	X	
Serum chemistry	X[i]	X[j k]	X[k l]	X[k l]	X[k l]	X[k l]	X[k l]	X[k l]	X[k l]	X[k l]	X[k l]	X[k l]	X	X	
Coagulation	X[i]	X[m]													
Pregnancy test[n]	X[i]	X[j k]											X	X	
HBV/HCV test[o]	X														
Serum-based tumor markers (e.g., CA125)[h]	X[i j]					X			X			X[h]	X		
Urinalysis	X[i j]			X[k l]			X[k l]			X[k l]		X[k l p]	X	X	
Thyroid panel[q]	X[i]		X		X		X		X		X	X	X		
ECG[r]	X[i]	X											X		
Physical examination	X[i]												X	X	
Symptom-directed PE[k]		X	X	X	X	X	X	X	X	X	X	X			
Vital signs, height, and weight[s]	X[i]	X	X	X	X	X	X	X	X	X	X	X	X		

Table 4: Part 2A Schedule of Events: Q3W Fixed-Dose Safety Evaluation Cohort (Continued)

Cycle/Visit:	Screening	Cycle 1[a]	Cycle 2[a]	Cycle 3[a]	Cycle 4[a]	Cycle 5[a]	Cycle 6[a]	Cycle 7[a]	Cycle 8[a]	Cycle 9[a]	Cycle 10[a]	Cycle n[a]	EOT[b]	Safety FUP[c]	FUP Assessments[d]
Day: Day: Procedure:	-35 to -1	1	1	1	1	1	1	1	1	1	1	1	30 ± 7 days	90 ± 7 days	(every 90± 14 days) via telephone
ECOG performance status	X		X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications	X														
AE monitoring	X[k t]														
Dostarlimab (TSR-042) administered[u]		X	X	X	X	X	X	X	X	X	X	X			
Survival assessment															X

Abbreviations: ADA=antidrug antibody; AE=adverse event; CBC=complete blood count; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End-of-treatment; FUP=follow-up; HBV=hepatitis B virus; HCV=hepatitis C virus; ICF=informed consent form; irRECIST=immune-related RECIST; IV=intravenous; MRI=magnetic resonance imaging; OC=ovarian cancer; PDy=pharmacodynamics; PE=physical examination; PK=pharmacokinetics; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event.
Note: All procedures are to take place within a ± 7 day window unless otherwise indicated.
[a] Treatment cycles are 21 ± 7 days in duration; one dose of dostarlimab will be administered on Day 1 of every cycle. One dose=one cycle.
[b] EOT visit should be completed 30 (±7) days after last study drug dose. Patients with ongoing AEs will be followed until resolution or stabilization of the AE.
[c] Safety follow-up visit should be conducted 90 (±7) days after last study drug dose or until initiation of new anticancer therapy, whichever comes first. Patients with ongoing AEs will be followed until resolution or stabilization of the AE.
[d] Follow up assessments should be conducted 90 (± 14) days after the last study drug dose. Survival and pregnancy status obtained at 90-day safety follow-up visit can be used for FUP assessment. Pregnancy status will be assessed through Day 150 post-treatment.
[e] The ICF may be signed prior to the 35-day screening period.
[f] Refer to Table 8 for the detailed sample collection schedule.
[g] For patients who consent to optional serial biopsies, the biopsies will be obtained prior to initiation of study treatment, 6 weeks following the first dostarlimab dose, EOT visit, and whenever possible, at the time of PD (note: while the biopsy is voluntary, it is highly encouraged). A core biopsy is recommended (details are provided in the Study Manual); if an excisional or incisional biopsy is to be performed, it must be conducted on a non-target lesion.
[h] Tumor assessment per irRECIST via CT or MRI (chest, abdomen, and pelvis) is required at screening, 12 weeks after the first dostarlimab dose (84 ±10 days), and every 6 weeks (42±10 days) thereafter while on study treatment independent of cycle delays and/or dose interruptions, and/or at any time when progression

of disease is suspected (a final set of radiographic images is required at the time of PD, if not done within the last 4 weeks). Appropriate testing of serum tumor markers (e.g., CA-125 for OC patients) should also be conducted 12 weeks after the first dostarlimab dose (84 ±10 days), and every 6 weeks (42±10 days) thereafter, and as clinically indicated. Brain scan will be conducted if clinically indicated. Bone scans will be conducted per standard of care. After 1 year, patients who remain on treatment will have imaging performed every 12 weeks (84 ±10 days). If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, imaging scans and appropriate serum-based tumor marker testing (e.g., CA-125 for OC patients) should continue at the specified intervals. Per irRECIST, complete response (CR) or partial response (PR) should be confirmed; tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated. In addition, PD should be confirmed a minimum of 4 weeks and up to 6 weeks after the first PD assessment. Clinically stable patients should not be discontinued until progression is confirmed (see Section 6.3.1.5 and Appendix B).

[i] Standard of care tests/procedures, scans, laboratory assessments, ECGs, physical examinations, vital signs, height, and weight performed prior to the patient signing the ICF can be used as part of the screening assessments as long as the tests/procedures meet the protocol-required timelines (i.e., within 35 days of first dose for these procedures with the exception of the pregnancy test, which must be conducted within 72 hours of first dose date).

[j] If screening laboratory testing (CBC, serum chemistry, serum-based tumor markers, urinalysis) performed within 72 hours prior to the date of first dose of study treatment on Day 1, repeat testing is not required.

[k] Sample collection/procedure must be performed prior to dostarlimab administration.

[l] Samples can be collected up to 72 hours prior to dostarlimab administration.

[m] To be conducted per standard of care for patients on anticoagulant therapy.

[n] Negative serum pregnancy test required within 72 hours prior to date of first dose of study treatment on Day 1 for females of childbearing potential; urine pregnancy test conducted at the 30-day EOT visit, and at the 90-day Safety FUP visit.

[o] Only when medically indicated based on history and physical examination.

[p] Urinalysis sample to be obtained on Day 1 of Cycle 12 and Day 1 of every third cycle thereafter (e.g., Cycle 15, 18, 21, 24, etc).

[q] Blood samples for thyroid panel (i.e., TSH, T3 or FT3, and FT4 or equivalent tests, where applicable) are to be collected starting on Cycle 2/Day 1 and every 6 weeks thereafter (blood samples can be collected up to 7 days prior to dostarlimab administration).

[r] Patients will undergo ECG monitoring at screening, Day 1 of Cycle 1, at EOT visit, and if clinically indicated.

[s] Vital signs include blood pressure, pulse, and temperature. Height obtained at screening only.

[t] AEs and SAEs are required to be captured through 90 days after cessation of study treatment (or until the start of alternate anticancer therapy, whichever occurs first), and any pregnancies that occur within 150 days post-treatment are to be captured.

[u] Administer dostarlimab on Day 1 of each cycle.

Table 5: Part 2A Schedule of Events: Q6W Fixed-Dose Safety Evaluation Cohort

Cycle/Visit:	Screening	Cycle 1[a]	Cycle 2[a]	Cycle 3[a]	Cycle 4[a]	Cycle 5[a]	Cycle 6[a]	Cycle n[a]	EOT[b]	Safety FUP[c]	FUP Assessments[d] (every 90 ± 14 days) via telephone
Day **Procedure:**	**-35 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**30 ± 7 days**	**90 ± 7 days**	
Informed consent[e]	X										
Inclusion/exclusion criteria review	X	X									
Demographics	X										
Medical, surgical, cancer, and medication history	X										
Blood sample for PK/ADA[f]		X[f]	X[f]	X[f]	X[f]	X[f]		X[f]		X[f]	
Blood sample for PDy[f]		X[f]	X[f]								
Blood sample for Exploratory biomarkers[f]		X[f]	X[f]	X[f]	X[f]	X[f]	X[f]		X[f]		
Optional Tumor Biopsy[g]	X		X						X		
Tumor assessment (irRECIST)[h]	X[i]			X	X	X	X	X[h]	X	X	
Laboratory assessments:											
CBC w/differential	X[i]	X[j k]	X[k l]	X[k l]	X[k l]	X[k l]	X[k l]	X[k l]	X	X	
Serum chemistry	X[i]	X[j k]	X[k l]	X[k l]	X[k l]	X[k l]	X[k l]	X[k l]	X	X	
Coagulation	X[i]	X[m]									
Pregnancy test[n]	X[i]	X[j k]							X	X	
HBV/HCV test[o]	X										
Serum-based tumor markers (e.g., CA125)[h]	X[i j]			X	X	X	X	X[h]	X		
Urinalysis	X[i j]			X[k l]			X[k l]	X[k l p]	X	X	
Thyroid panel[q]	X[i]		X	X	X	X	X	X[q]	X		
ECG[r]	X[i]	X							X		
Physical examination	X[i]								X	X	
Symptom-directed PE[k]		X	X	X	X	X	X	X			
Vital signs, height, and weight[s]	X[i]	X	X	X	X	X	X	X	X		

Cycle/Visit:	**Screening**	**Cycle 1[a]**	**Cycle 2[a]**	**Cycle 3[a]**	**Cycle 4[a]**	**Cycle 5[a]**	**Cycle 6[a]**	**Cycle n[a]**	**EOT[b]**	**Safety FUP[c]**	**FUP Assessments[d] (every 90 ± 14 days) via telephone**
Day **Procedure:**	**-35 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**30 ± 7 days**	**90 ± 7 days**	
ECOG performance status	X		X	X	X	X	X	X	X		
Concomitant medications	X										
AE monitoring	X[k t]										
Dostarlimab (TSR-042) administered[u]		X	X	X	X	X	X	X			
Survival assessment											X

Abbreviations: ADA=antidrug antibody; AE=adverse event; CBC=complete blood count; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End-of-treatment; FUP=follow-up; HBV=hepatitis B virus; HCV=hepatitis C virus; ICF=informed consent form; irRECIST=immune-related RECIST; IV=intravenous; MRI=magnetic resonance imaging; OC=ovarian cancer; PDy=pharmacodynamics; PE=physical examination; PK=pharmacokinetics; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event.
Note: All procedures are to take place within a ± 7 day window unless otherwise indicated.

[a] Treatment cycles are 42 ± 7 days in duration; one dose of dostarlimab will be administered on Day 1 of every cycle. One dose=one cycle.

[b] EOT visit should be completed 30 (±7) days after last study drug dose. Patients with ongoing AEs will be followed until resolution or stabilization of the AE.

[c] Safety follow-up visit should be conducted 90 (±7) days after last study drug dose or until initiation of new anticancer therapy, whichever comes first. Patients with ongoing AEs will be followed until resolution or stabilization of the AE.

[d] Follow up assessments should be conducted 90 (± 14) days after the last study drug dose. Survival and pregnancy status obtained at 90-day safety follow-up visit can be used for FUP assessment. Pregnancy status will be assessed through Day 150 post-treatment.

[e] The ICF may be signed prior to the 35-day screening period.

[f] Refer to Table 9 for the detailed sample collection schedule.

[g] For patients who consent to optional serial biopsies, the biopsies will be obtained prior to initiation of study treatment, 6 weeks following the first dostarlimab dose, EOT visit, and whenever possible, at the time of PD (note: while the biopsy is voluntary, it is highly encouraged). A core biopsy is recommended (details are provided in the Study Manual); if an excisional or incisional biopsy is to be performed, it must be conducted on a non-target lesion.

[h] Tumor assessment per irRECIST via CT or MRI (chest, abdomen, and pelvis) is required at screening, 12 weeks after the first dostarlimab dose (84 ±10 days), and every 6 weeks (42±10 days) thereafter while on study treatment independent of cycle delays and/or dose interruptions, and/or at any time when progression of disease is suspected (a final set of radiographic images is required at the time of PD, if not done within the last 4 weeks). Appropriate testing of serum tumor markers (e.g., CA-125 for OC patients) should also be conducted 12 weeks after the first dostarlimab dose (84 ±10 days), and every 6 weeks (42±10 days) thereafter, and as clinically indicated. Brain scan will be conducted if clinically indicated. Bone scans will be conducted per standard of care. After 1 year, patients who remain on treatment will have imaging performed every 12 weeks (84 ±10 days). If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, imaging scans and appropriate serum-based tumor marker testing (e.g., CA-125 for OC patients) should continue at the specified intervals. Per irRECIST, complete response (CR) or partial response (PR) should be confirmed; tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated. In addition, PD should be confirmed a minimum of 4 weeks and up to 6 weeks after the first PD assessment. Clinically stable patients should not be discontinued until progression is confirmed (see (see Section 6.3.1.5 and Appendix B).

[i] Standard of care tests/procedures, scans, laboratory assessments, ECGs, physical examinations, vital signs, height, and weight performed prior to the patient signing the ICF can be used as part of the screening assessments as long as the tests/procedures meet the protocol-required timelines (i.e., within 35 days of first dose for these procedures with the exception of the pregnancy test, which must be conducted within 72 hours of first dose date).
[j] If screening laboratory testing (CBC, serum chemistry, serum-based tumor markers, urinalysis) performed within 72 hours prior to the date of first dose of study treatment on Day 1, repeat testing is not required.
[k] Sample collection/procedure must be performed prior to dostarlimab administration.
[l] Samples can be collected up to 72 hours prior to dostarlimab administration.
[m] To be conducted per standard of care for patients on anticoagulant therapy.
[n] Negative serum pregnancy test required within 72 hours prior to date of first dose of study treatment on Day 1 for females of childbearing potential; urine pregnancy test conducted at the 30-day EOT visit, and at the 90-day Safety FUP visit.
[o] Only when medically indicated based on history and physical examination.
[p] Urinalysis sample to be obtained on Day 1 of Cycle 12 and Day 1 of every third cycle thereafter (e.g., Cycle 15, 18, 21, 24, etc).
[q] Blood samples thyroid panel (i.e., TSH, T3 or FT3, and FT4 or equivalent tests, where applicable) are to be collected starting on Cycle 2/Day 1and every 6 weeks thereafter (blood samples can be collected up to 7 days prior to dostarlimab administration).
[r] Patients will undergo ECG monitoring at screening, Day 1 of Cycle 1, at EOT visit, and if clinically indicated.
[s] Vital signs include blood pressure, pulse, and temperature. Height obtained at screening only.
[t] AEs and SAEs are required to be captured through 90 days after end of treatment (or until the start of alternate anticancer therapy, whichever occurs first), and any pregnancies that occur within 150 days post-treatment are to be captured.
[u] Administer dostarlimab on Day 1 of each cycle.

Table 6: Part 2B Schedule of Events: Expansion Cohorts

	Q3W Dose Schedule					Q6W Dose Schedule									
Cycle/Visit:	**Screening[a]**	**Cycle1[a]**	**Cycle 2[a]**	**Cycle 3[a]**	**Cycle 4[a]**	**Cycle 5[a]**	**Cycle 6[a]**	**Cycle 7[a]**	**Cycle 8[a]**	**Cycle 9[a]**	**Cycle 10[a]**	**Cycle n[a]**	**EOT[b]**	**Safety FUP[c]**	**FUP Assessments (every 90±14 days)**
Day: **Day:** **Procedure:**	**-35 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**30 or 42±7 days**	**90±7 days**	
Informed consent[d]	X														
Inclusion/exclusion criteria review	X	X													
Demographics	X														
Medical, surgical, cancer, and medication history	X														
Blood sample for PK/ADA[e]		X			X	X			X			X		X	
Blood sample for exploratory biomarkers[e]		X	X	X	X	X	X						X		
Blood sample for exploratory ctDNA[e]		X													
Blood sample for MSI testing (Cohort A1, A2, and F only)[e]		X													
Required Tumor Biopsy[f]	X														
Optional Tumor Biopsy[g]	X			X									X		

	Q3W Dose Schedule					Q6W Dose Schedule									
Cycle/Visit:	**Screening[a]**	**Cycle1[a]**	**Cycle 2[a]**	**Cycle 3[a]**	**Cycle 4[a]**	**Cycle 5[a]**	**Cycle 6[a]**	**Cycle 7[a]**	**Cycle 8[a]**	**Cycle 9[a]**	**Cycle 10[a]**	**Cycle n[a]**	**EOT[b]**	**Safety FUP[c]**	**FUP Assessments (every 90±14 days)**
Day: **Day:** **Procedure:**	**-35 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**30 or 42±7 days**	**90±7 days**	
Tumor assessment (irRECIST)[h]	X[h]					X	X	X	X	X	X	X	X[h]	X	
PRO assessments (Cohorts A1 and F)[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments:															
CBC w/differential	X[j]	X[kl]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X	X	
Serum chemistry	X[j]	X[kl]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X	X	
Coagulation	X[j]	X[m]													
Pregnancy test	X[j]	X[kln]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	
HBV/HCV test[o]	X														
Serum-based tumor markers (eg, CA125)	X[jk]					X	X	X	X	X	X	X	X		
Urinalysis	X[jk]			X[l]		X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X	X	
Thyroid panel[p]	X[j]		X		X		X	X	X	X	X	X	X		
ECG[q]	X[jq]	X[q]			X[q]	X[q]			X[q]			X[q]	X[q]		
Physical examination	X[j]												X	X	
Sympto m-		X	X	X	X	X	X	X	X	X	X	X			

	Q3W Dose Schedule					Q6W Dose Schedule									
Cycle/Visit:	**Screening[a]**	**Cycle1[a]**	**Cycle 2[a]**	**Cycle 3[a]**	**Cycle 4[a]**	**Cycle 5[a]**	**Cycle 6[a]**	**Cycle 7[a]**	**Cycle 8[a]**	**Cycle 9[a]**	**Cycle 10[a]**	**Cycle n[a]**	**EOT[b]**	**Safety FUP[c]**	**FUP Assessments (every 90±14 days)**
Day: **Day:** **Procedure:**	**-35 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**30 or 42±7 days**	**90±7 days**	
directed PE[l]															
Vital signs, height, and weight[r]	X[j]	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG performance status	X		X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications	X														
AE monitoring	X[s]														
Dostarlimab (TSR-042) administered[t]		X	X	X	X	X	X	X	X	X	X	X			
Survival follow up and post-study new cancer therapy assessment														X	X[u]

Abbreviations: ADA=antidrug antibody; AE=adverse event; CBC=complete blood count; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End-of-treatment; FUP=follow-up; HBV=hepatitis B virus; HCV=hepatitis C virus; ICF=informed consent form; irRECIST=immune-related RECIST; IV=intravenous; MRI=magnetic resonance imaging; MSI=microsatellite instability; OC=ovarian cancer; PE=physical examination; PK=pharmacokinetics; Q3W=every 3 weeks; Q6W=every 6 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event.

[a] Treatment cycles are 21 ± 7 days in duration for Cycle 1 through Cycle 4. Treatment cycles are 42 ± 7 days in duration for Cycle 5 and all subsequent cycles. One dose of dostarlimab will be administered on Day 1 of every cycle. One dose=one cycle.

[b] EOT visit should be completed 30 days (Q3W schedule) or 42 days (Q6W schedule) (±7) days after last study drug dose. Patients with ongoing AEs will be followed until resolution or stabilization of the AE.

[c] Safety follow-up visit should be conducted 90 (±7) days after last study drug dose unless new anticancer therapy, has been initiated. Patients with ongoing AEs will be followed until resolution or stabilization of the AE.

[d] The ICF may be signed prior to the 35-day screening period.

[e] Refer to Table 10 for the detailed sample collection schedule.

[f] Patients are required to have tumor tissue available (archival or newly obtained biopsy) prior to start of study treatment. Patients can be screened based on local MMR/MSI testing results using IHC, PCR, or NGS performed in a certified local laboratory, but patient eligibility needs to be determined by MMR IHC results. For patients with available local MMR IHC results for the respective cohort(s), tumor samples have to be submitted to a central IHC laboratory and its quality has to be checked and cleared prior to C1D1. For patients without available local MMR IHC test results (patients with local PCR or NGS test results), tumor samples have to be submitted directly to central IHC laboratory and central IHC results have to confirm eligibility prior to proceeding with other screening procedures. After the central IHC test is completed, remaining tumor tissue may be sent to a central NGS laboratory for further testing.

[g] For patients who consent to optional serial biopsies, the biopsies will be obtained prior to initiation of study treatment, approximately 4-6 weeks following the first dostarlimab dose, EOT visit, and whenever possible, at the time of PD (note: while the biopsy is voluntary, it is highly encouraged). A core biopsy is recommended (details are provided in the Study Manual); if an excisional or incisional biopsy is to be performed, it must be conducted on a non-target lesion. If a patient has had a biopsy prior to screening and within 12 weeks of study treatment, that biopsy may be accepted as the screening biopsy.

[h] Tumor assessment per irRECIST via CT or MRI (chest, abdomen, and pelvis) is required at screening within 28 days of the first dose, 12 weeks after the first dostarlimab dose (84 ±10 days), and every 6 weeks (42 ±10 days) thereafter while on study treatment independent of cycle delays and/or dose interruptions, and/or at any time when progression of disease is suspected (a final set of radiographic images is required at the time of PD, if not done within the last 4 weeks). Appropriate testing of serum tumor markers (e.g., CA-125 for OC patients) should also be conducted 12 weeks after the first dostarlimab dose (84 ±10 days), and every 6 weeks (42 ±10 days) thereafter, and as clinically indicated. Brain scan will be conducted if clinically indicated. Bone scans will be conducted per standard of care. After 1 year, patients who remain on treatment will have imaging performed every 12 weeks (84 ±10 days). If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, imaging scans and appropriate serum-based tumor marker testing (e.g., CA-125 for OC patients) should continue at the specified intervals. All radiographic images/scans will be sent to a central imaging vendor upon acquisition and archived for potential future evaluation. Per irRECIST, complete response (CR) or partial response (PR) should be confirmed; tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated. If new response (ie, CR or PR) is seen after 1 year, a confirmatory scan should be conducted between 4-6 weeks after the new response was first observed. In addition, it is highly recommended that PD should be confirmed a minimum of 4 weeks and up to 6 weeks after the first PD assessment. Clinically stable patients should not be discontinued until progression is confirmed (see Section 6.3.1.5 and Appendix B).

[i] PROs should be collected before conducting any other procedures and will be performed only for patients in Cohorts A1 and F enrolled under Amendment 3 or subsequent amendments. After Safety Follow-up visit, PROs may be conducted via telephone.

[j] Standard of care tests/procedures, scans, laboratory assessments, ECGs, physical examinations, vital signs, height, and weight performed prior to the patient signing the ICF can be used as part of the screening assessments as long as the tests/procedures meet the protocol-required timelines (i.e., within 35 days of first dose for these procedures with the exception of the pregnancy test, which must be conducted within 72 hours of first dose date, and the baseline tumor assessments scans, which must be done within 28 days of the first dose) and any relevant guidelines (e.g., diagnostic quality for scans).

[k] If screening assessments (except for physical examination, symptom-directed PE and vital signs) are performed within 72 hours prior to the date of first dose of study treatment on Day 1, repeat assessment is not required. Unless screening labs were done within 72 hours of C1D1, C1D1 laboratory results should meet the eligibility criteria

[l] Sample collection/procedure can be performed up to 72 hours prior to dostarlimab administration.

[m] To be conducted per standard of care for patients on anticoagulant therapy.

[n] Negative serum pregnancy test required within 72 hours prior to date of the first dose of study treatment on Day 1 for females of childbearing potential; urine or serum pregnancy test must be conducted within 72 hours prior to the first dose of study treatment on Day 1 of every cycle for the duration of the study, at the

30-day (Q3W schedule) or 42-day (Q6W schedule) EOT visit, and at the 90-day Safety FUP visit. Pregnancy status obtained at 90-day safety follow-up visit can be used for FUP assessment. Pregnancy status will be reported through Day 150 post-treatment.

[o] Only when medically indicated based on history and physical examination.

[p] Blood samples for the thyroid panel (i.e., TSH, T3 or FT3, FT4, or equivalent tests) are to be collected during screening, Cycle 2/Day 1, Cycle 4/Day 1, Cycle 6/Day 1, and every 6 weeks thereafter through the remainder of the study (blood samples can be collected up to 7 days prior to dostarlimab administration).

[q] Patients will undergo ECG monitoring by 12-lead ECG evaluations with triplicate readouts at screening, pre-dose and at 0.5h (end of infusion ± 30 minutes) on Day 1 of Cycles 1, 4, 5, 8, and 12, at the EOT visit, and if clinically indicated.

[r] Vital signs include blood pressure, pulse, and temperature. Height obtained at screening only.

[s] AEs and SAEs are required to be captured through 90 days after end of treatment visit (or until the start of alternate anticancer therapy, whichever occurs first), and any pregnancies that occur within 150 days post-treatment are to be reported.

[t] Administer dostarlimab on Day 1 of each cycle.

[u] Follow up assessments should be conducted over telephone every 90 (± 14) days after the last study drug dose. Survival status obtained at 90-day safety follow-up visit can be used for FUP assessment.

Table 7: Part 1 Pharmacokinetic Sampling Schedule

Visit/Cycle:	Cycle 1[a]							Cycles 1[a], 2, 3, 4 and 5		Cycle 6					Cycles 8+[b]	Safety FUP: 90±7 days
Study Day:	**1**	**2**	**3**	**5**	**8**	**15**	**22**	**1**	**15**	**1**	**2**	**5**	**8**	**15**	**1**	
Time relative to start of dostarlimab (TSR-042) 30-minute IV infusion																
Predose (within 30 min)	X							X[c]	X	X				X[d]	X	
0.25 hr (±2 min)	X							X	X	X				X		
0.5 hr (±5 min)[e]	X							X	X	X				X		
1.5 hr (±5 min)	X									X						
3 hr (±5 min)	X									X						
24 hr (±2 hrs)		X									X					
48 hr (±4 hrs)			X													
96 hr (±24 hrs)				X								X				
168 hr (±24 hrs)					X								X			
336 hr (±24 hrs)[d]						X[a]								--[d]		
504 hr (±24 hrs)							X									
672 hr (±24 hrs) [c]								--[c]								
Safety Follow-up visit																X

Abbreviations: hr(s)=hour(s); FUP=follow-up; IV=intravenous; min=minute.

[a] For patients with Cycle 1/Day 15 dose, Sample (336 ±24 hr) is the last sampling point for Cycle 1/Day 1 and can be drawn predose (within 30 min) on Cycle 1/Day 15. Three samples (predose, 0.25 hr and 0.5 hr post start of infusion) will be drawn on Cycle 1/Day 15. For DLT-evaluable patients, Cycle 1 will have 2 doses, one on Day 1 and one on Day 15.

[b] Predose (within 30 min) sample to be obtained on Day 1 of Cycle 8 and every other cycle thereafter (eg, Cycles 10, 12, etc).

[c] For Cycle 2/Day 1, the predose (within 30 min) sample can be the same sample as the 672 hr (±24 hr) sample post-dose on Cycle 1/Day 1.

[d] For Cycle 6/Day 15, the predose (within 30 min) sample can be the same sample as the 336 hr (±24 hr) sample post-dose on Cycle 6/Day 1.

[e] Sample to be obtained at the end of the planned 30-min IV infusion (±5 minutes).

Table 8: Part 2A PK/PDy Sampling Schedule: Q3W Fixed-Dose Safety Evaluation Cohort

Visit/Cycle:	Cycle 1							Cycles 2, 3, and 4	Cycle 5							Cycles 6+[a]	EOT 30±7 days	Safety FUP: 90±7 days
Study Day:	**1**	**2**	**3**	**5**	**8**	**15**	**22**	**1**	**1**	**2**	**3**	**5**	**8**	**15**	**22**	**1**		
Time relative to start of dostarlimab (**TSR-042**) **30-minute IV infusion**																		
Predose (within 30 min)	X							X	X							X		
0.25 hr (±2 min)	X							X	X									
0.5 hr (±5 min)[b]	X							X	X									
1.5 hr (±5 min)	X								X									
3 hr (±5 min)	X								X									
24 hr (±2 hrs)		X								X								
48 hr (±4 hrs)			X								X							
96 hr (±24 hrs)				X								X						
168 hr (±48 hrs)					X								X					
336 hr (±48 hrs)						X								X				
504 hr (±48 hrs)							X[c]								X[d]			
Safety Follow-up visit																		X
Blood sample for PDy	X[e]			X		X		X[e f]										
Blood sample for exploratory biomarkers	X[e]					X		X[e]	X[e]							X[e g]	X	

Abbreviations: EOT=end of treatment; hr(s)=hour(s); FUP=follow-up; IV=intravenous; min=minute; PDy=pharmacodynamics; PK=pharmacokinetics; Q3W=every 3 weeks.

[a] Predose (within 30 min) sample to be obtained on Day 1 of Cycle 6 and every 3 cycles thereafter (e.g., Cycles 9, 12, 15, etc).

[b] Sample to be obtained at the end of the planned 30-min IV infusion (±5 minutes).

[c] Sample must be collected if the study drug administration in Cycle 2 is delayed beyond the permitted time window. If there are no delays in Cycle 2 dosing, sample does not need to be collected since the predose sample on Cycle 2/Day 1 is considered the same as the 504 hr post-dose sample in Cycle 1.

[d] Sample must be collected if the study drug administration in Cycle 6 is delayed beyond the permitted time window. If there are no delays in Cycle 6 dosing, sample does not need to be collected since the predose sample on Cycle 6/Day 1 is considered the same as the 504 hr post-dose sample in Cycle 5.

[e] Sample to be obtained up to 2 hours prior to dostarlimab dose.

[f] Sample to be obtained on Cycle 2/Day 1 only.

[g] Sample to be obtained on Cycle 6/Day 1 only.

Table 9: Part 2A PK/PDy Sampling Schedule: Q6W Fixed-Dose Safety Evaluation Cohort

Visit/Cycle:	Cycle 1										Cycles 2 and 3	Cycle 4										Cycle 5+[a]	EOT 30±7 days	Safety FUP: 90±7 days
Study Day:	**1**	**2**	**3**	**5**	**8**	**15**	**22**	**29**	**36**	**43**	**1**	**1**	**2**	**3**	**5**	**8**	**15**	**22**	**29**	**36**	**43**	**1**		
Time relative to start of dostarlimab (**TSR-042) 30-minute IV infusion**																								
Predose (within 30 min)	X										X	X										X		
0.25 hr (±2 min)	X										X	X												
0.5 hr (±5 min)[b]	X										X	X												
1.5 hr (±5 min)	X											X												
3 hr (±5 min)	X											X												
24 hr (±2 hrs)		X											X											
48 hr (±4 hrs)			X											X										
96 hr (±24 hrs)				X											X									
168 hr (±48 hrs)					X											X								
336 hr (±48 hrs)						X											X							
504 hr (±48 hrs)							X											X						
672 hr (±48 hrs)								X											X					
840 hr (±48 hrs)									X											X				
1008 hr (±48 hrs)										X[c]											X[d]			
Safety Follow-up visit																								X
Blood sample for PDy	X[e]			X		X		X			X[e f]													
Blood sample for exploratory biomarkers	X[e]					X					X[e]	X[e]										X[e g]	X	

Abbreviations: EOT=end of treatment; hr(s)=hour(s); FUP=follow-up; IV=intravenous; min=minute; PDy=pharmacodynamics; PK=pharmacokinetics; Q6W=every 6 weeks.

[a] Predose (within 30 min) sample to be obtained on Day 1 of Cycle 5 and Day 1 of every other three cycles thereafter (e.g., Cycles 8, 11, 14, etc).

[b] Sample to be obtained at the end of the planned 30-min IV infusion (±5 minutes).

[c] Sample must be collected if the study drug administration in Cycle 2 is delayed beyond the permitted time window. If there are no delays in Cycle 2 dosing, sample does not need to be collected since the predose sample on Cycle 2/Day 1 is considered the same as the 1008 hr post-dose sample in Cycle 1.

[d] Sample must be collected if the study drug administration in Cycle 5 is delayed beyond the permitted time window. If there are no delays in Cycle 5 dosing, sample does not need to be collected since the predose sample on Cycle 5/Day 1 is considered the same as the 1008 hr post-dose sample in Cycle 4.
[e] Sample to be obtained up to 2 hours prior to dostarlimab dose.
[f] Sample to be obtained on Cycle 2/Day 1 only.
[g] Sample to be obtained on Cycle 5/Day 1 and Cycle 6/Day 1 only.

Table 10: Part 2B PK Sampling Schedule: Expansion Cohorts

	Q3W Dose Schedule				Q6W Dose Schedule				
Visit/Cycle:	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycles 8 and 12**	**EOT 30 or 42±7 days**	**Safety FUP: 90±7 days**
Study Day:	**1**	**1**	**1**	**1**	**1**	**1**	**1**		
Time relative to start of dostarlimab (TSR-042) 30-minute IV infusion									
Predose (within 30 min)	X			X	X		X		
0.5 hr (±5 min)[a]	X			X	X		X		
1.5 hr (±30 min)	X			X	X		X		
Safety Follow-up visit									X
Blood sample for exploratory biomarkers	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]		X	
Blood sample for exploratory ctDNA	X[b]								
Blood sample for MSI and POLE testing (Cohorts A1, A2, and F)	X[b]								

Abbreviations: ctDNA= circulating tumor DNA; EOT=end of treatment; hr(s)=hour(s); FUP=follow-up; IV=intravenous; min=minute; MSI=microsatellite instability; PK=pharmacokinetics.

[a] Sample to be obtained at the end of the planned dostarlimab 30-min IV infusion (±5 minutes).

[b] Sample to be obtained up to 2 hours prior to dostarlimab dose

7.2. Procedures by Visit

Standard of care tests/procedures, including laboratory assessments, ECG, physical examination, vital signs, height, and weight, performed prior to the patient signing the ICF can be used as part of the screening assessments as long as the tests/procedures meet the protocol-required timelines (i.e., within 21 or 35 days of first dose for Part 1 or Part 2, respectively, with the exception of the pregnancy test which must be conducted within 72 hours of first dose date). If screening assessments (except for physical examination, symptom-directed PE and vital signs) are performed within 72 hours prior to the date of first dose of study treatment on Day 1, repeat assessment is not required. Unless screening labs were done within 72 hours of C1D1, C1D1 laboratory results should meet the eligibility criteria. Scans performed prior to informed consent as part of routine clinical management are also acceptable for use as initial tumor imaging if they are of diagnostic quality and are performed within 21 or 28 days prior to first dose date for Part 1 or Part 2, respectively. Note that source documents must clearly identify the standard of care tests/procedures that are used for screening and the results of these tests/procedures must be entered in the eCRF.

Refer to Table 3 (Part 1), Table 4 (Part 2A Q3W), Table 5 (Part 2A Q6W), Table 6 (Part 2B) and for a detailed summaries of the events performed during the study. Table 7 (Part 1), Table 8 (Part 2A Q3W), Table 9 (Part 2A Q6W), and Table 10 (Part 2B) present the PK/PDy sampling schedules.

8. STATISTICAL METHODS

Details of the statistical analyses presented below will be provided in the study's statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the plan will be described and justified in the final clinical study report.

8.1. Study Populations

Six analysis populations will be defined as follows:

- Safety Population (SAF): All patients who receive any amount of study drug.

  For dose escalation decision purposes, the assessment of DLTs will include

  - Part 1: Only those patients who received 2 doses of dostarlimab (i.e., on Cycle 1/Day 1 and Cycle 1/Day 15) and completed the safety evaluations throughout Cycle 1 (i.e., 28 days) or patients who discontinued study drug during Cycle 1 due to a DLT.
  - Part 2A: Only those patients who received one dose of dostarlimab and completed the safety evaluations throughout Cycle 1 (i.e., 21 days for the Q3W cohort and 42 days for the Q6W cohort) or patients who discontinued study drug during cycle 1 due to a DLT
- Efficacy Population:
  - Part 1 and Part 2A: All patients who received any amount of study drug.
  - dMMR/MSI-H EC patients from Cohort A1 and as well as retrospectively identified dMMR EC patients from Cohort A2 in Part 2B: All patients in Safety Population with measurable disease at baseline (defined as the existence of at least one target lesion) who have dMMR status based on MMR/MSI testing result using IHC (local or central) OR MMR status unknown with MSI-H based on local or central MSI testing results using PCR or NGS.
  - [redacted]

[redacted]

- Per Protocol Population (PP): All patients in the Efficacy Population who have measurable disease at baseline and have no significant protocol deviations during the study.
- PK population: All patients who receive at least 1 dose of study drug and have at least one PK sample.
- Antidrug-Antibody population: All patients who receive at least 1 dose of study drug and have provided the pre-treatment blood sample and at least one post-treatment serum sample at or after 96 hours.
- PRO population: All patients in Cohorts A1 [redacted] enrolled under Amendment 3 and subsequent amendments, who have completed both baseline and at least 1 post-baseline PRO assessment.

8.2. Demographics, Medical History, Baseline Characteristics, and Concomitant Medications

Demographics, baseline characteristics, and medical history information will be summarized for the Safety population using descriptive statistics by

- dose level for Part 1 and Part 2A
- [redacted] and/or MMR status (dMMR, MMR-proficient and MMR unknown) for Cohorts A1, [redacted] in cohort for Part 2B.

No formal statistical comparisons will be performed.

Demographic, baseline characteristics, and medical history data for each patient will be provided in data listings.

8.3. Safety Analyses

The analysis set for the safety endpoint will be the safety population.

The following key safety parameters will be evaluated by dose level for Part 1 and Part 2A, by [redacted] and/or MMR status (dMMR, MMR-proficient and MMR unknown) for Cohorts A1, [redacted] in cohort for Part 2B, unless noted otherwise:

- Dose-limiting toxicities during the DLT observation period in Part 1 and Part 2A
- Incidence of TEAEs, immune-related AEs of interest (irAEIs), and SAEs occurring while patients are on treatment or up to 90 days after the end of treatment visit
- Changes in clinical laboratory parameters (hematology, chemistry, thyroid function, coagulation, urinalysis), CTCAE graded laboratory toxicities, vital signs, ECOG performance status, ECG parameters, physical examinations, and usage of concomitant medications

All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) coding system and displayed in tables and data listings using system organ

class (SOC) and preferred term (PT). Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined per protocol as any new AE that begins, or any preexisting condition that worsens in severity, after at least 1 dose of study treatment has been administered and throughout the treatment period until 90 days after end of treatment visit (or until the start of alternate anticancer therapy, whichever occurs earlier)

DLTs will be tabulated by dose level in Part 1 and Part 2A.

The number and percentage of patients with any TEAE assessed by the Investigator as related to treatment (definite, probable, or possible relationship), and with any SAE will be summarized by dose level for Part 1 and Part 2A, [redacted] MMR status (dMMR, MMR-proficient and MMR unknown) for Cohorts A1, [redacted] in Part 2B. In these tabulations, each patient will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes. No formal hypothesis-testing analysis of AE incidence rates will be performed.

The occurrence of and reasons for any requirement for dose interruption will be tabulated.

All AEs occurring on-study will be listed in patient data listings. By-patient listings also will be provided for the following: patient deaths, SAEs, and AEs leading to withdrawal.

8.4. Pharmacokinetic Analyses

The analysis set for the pharmacokinetic parameters will be the PK population.

Pharmacokinetic parameters to be determined will include $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, AUC_{ss}, C_{min}, C_{max}, CL, V_z, $C_{min,ss}$, and $C_{max,ss}$. Serum concentrations and PK parameter estimates will be presented using descriptive statistics by dose and regime. Summary statistics will include mean, standard deviation, coefficient of variation (CV), geometric mean, geometric mean CV, median, minimum, and maximum.

8.5. Antidrug-Antibody Analyses

The analysis set for antidrug-antibody analyses will be antidrug-antibody population.

The number and percent of patients who become positive for ADAs and who develop neutralizing antibodies will be summarized by visit/time and overall.

8.6. Efficacy Analyses

The primary analysis set for the efficacy endpoints will be the efficacy population. Objective response rates will in addition be calculated in the PP population for Part 2B.

All efficacy endpoints will be summarized on the data from patients in Part 2B by [redacted] MMR status (dMMR, MMR-proficient and MMR unknown) for Cohorts A1, [redacted]. Results from local or central MMR/MSI and local or central POLE testing will be used to determine the MMR/MSI and POLE status for Cohorts A1, [redacted] for efficacy analysis.

All analyses will include summary statistics, including number of patients (n) and percentage (%) for categorical variables and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided exact 95% confidence intervals

(CIs) based on the Clopper-Pearson method[58] will be provided where appropriate. Time-to-event analyses will be performed using Kaplan-Meier (KM) methods.

As the Part 2B portion of the study is single-arm, any statistical analysis to be performed among subgroups is for descriptive and future study purposes.

8.6.1. Primary Efficacy Parameter

The primary efficacy endpoint will be ORR, defined as the achievement of CR or PR

- Cohorts A1, A2, and F in Part 2B: Independent blinded central review using RECIST v1.1
- Part 1, Part 2A, and Cohort E in Part 2B: Investigators' assessment using irRECIST

The number and proportion of ORR and irORR will be tabulated by dose level for Part 1 and Part 2A [redacted] MMR status (dMMR, MMR-proficient and MMR unknown) for Part 2B (Cohorts A1, [redacted], along with 2-sided exact 95% CIs. No multiplicity adjustment will be made since separate inferences will be drawn for each cohort.

8.6.2. Secondary Efficacy Parameter(s)

Disease control rate will be assessed as a secondary endpoint and is defined as the proportion of patients achieving CR, PR, or SD as assessed

- Cohorts A1, [redacted] Part 2B: Independent blinded central review using RECIST v1.1
- Part 1, [redacted], in Part 2B: Investigators' assessment using irRECIST

The number and proportion of DCR (Cohorts A1, [redacted]) and irDCR will be tabulated by dose level for Part 1 and Part 2A [redacted] MMR status (dMMR, MMR-proficient and MMR unknown) for Part 2B using descriptive statistics including the number, percentage, and 2-sided exact 95% CIs.

For Part 1 and Part2A, irDOR, irPFS and OS will be presented in listings only due to small sample sizes in each dose level.

For Part 2B, DOR (Cohorts A1, [redacted]), irDOR, PFS (Cohorts A1, [redacted]), irPFS and OS will be presented through use of summary statistics using KM methods, to include 25th, 50th (median), and 75th percentiles and associated 2-sided 95% CIs for the median, number of events and number of censored observations. Specific censoring rules will be provided in detail in the statistical analysis plan (SAP).

8.7. PRO Analyses

For patients in Cohorts A1 [redacted] enrolled under Amendment 3 and subsequent amendments, actual values and observed changes from baseline in the PROs assessments (EQ-5D-5L and EORTC QLQ-C30) will be calculated and summarized by timepoint using descriptive statistics.

8.8. Biomarker Analyses

For each patient in the study, blood and tumor samples may be prospectively collected, evaluated and archived to support exploratory biomarker analysis. PD-L1 expression (retrospective

analysis), immune cell infiltrates, and/or other exploratory biomarkers may be correlated with response. Tumor genomic alterations (e.g., MMR/MSI and POLE) may be correlated with other immune-related biomarkers and with clinical activity in Part 2.

8.9. Determination of Sample Size

Sample size calculations were performed using SAS® version 9.4.

Part 1: A total sample size of approximately 36 patients is expected, but this may increase to approximately 54 patients, for the dose escalation portion of the study to provide incidence of DLTs as well as the safety and PK/PDy profile of dostarlimab.

Part 2A: A total sample size of approximately 12 patients is expected, but this may increase up to 24 patients, depending on the number of DLTs observed

Part 2B: A total sample size of up to 680 patients is estimated for the expansion portion of this study to provide assessment of clinical activity of dostarlimab based on ORR.

Cohort A1 will enroll approximately 100 with the potential for up to 165 patients with dMMR/MSI-H EC, [redacted]

Adjustments to enrollment within cohorts may occur based on emerging data and Sponsor's decision.

For Cohort A1 in Part 2B, the null hypothesis that the true response rate is ≤20% (H0: $p \leq 0.2$) will be tested against a one-sided alternative of ≥40% (Ha: $p \geq 0.4$). With 65 subjects treated, the cohort has 92% power to rule out a ≤ 20% ORR (null hypothesis) when the true ORR is 40% at the 2.5% type I error rate (one-sided). Of note, given a recent report where 6 of 9 patients with MSI endometrial cancer achieved a clinical response following treatment with an anti-PD-1 antibody, the activity of dostarlimab in this patient population is expected to negate the necessity for a two-stage design and thus there will not be an interim analysis in this cohort.

The sample size of Cohort A1 will be increased to 100 patients which will allow the lower-limit boundary of the exact 95% confidence interval excluding a response rate of 25% or less and assuming observed ORR is 35%.

[redacted]

[redacted]

Table 11: Observed ORR with Exact 95% CI

Observed ORR	95% Exact CI
5%	(1.8% - 10.2%)
10%	(5.7% - 17.1%)
15%	(9.4% - 22.7%)
20%	(13.4% - 28.1%)
22%	**(15.4% - 30.7%)**
25%	(17.5% - 33.3%)
30%	(22.5% - 39.3%)

[redacted]

8.10. Interim Analysis

For Part 1, the trial data was evaluated before a decision was made to go to the next dose level.

For Part 2B, the number of responses will be counted based on investigators' assessment using irRECIST and both confirmed and unconfirmed responses will be included.

[redacted]

9. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

9.1. Data Quality Assurance

The Sponsor (or designee) will conduct a study initiation visit to verify the qualifications of the Investigator, inspect the facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an ongoing basis. The Sponsor's Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to GCP and standard operating procedures for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Principal Investigator.

9.2. Access to Source Data/Documents

An electronic data capture system to manage data collection will be utilized during this trial. The electronic data capture system is a software tool designed to ensure quality assurance and facilitate data capture during clinical trials. The system is fully compliant with Code of Federal Regulations 21 Part 11.

The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The Investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE, and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each patient receiving study treatment.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB to have direct access to all documents pertaining to the study.

9.3. Archiving Study Documents

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study,

maintained for the duration of the study, and retained according to the appropriate regulations. According to International Council on Harmonization (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment.

9.4. Good Clinical Practice

This study will be conducted in accordance with the ICH for GCP and the Declaration of Helsinki (Version 2008). The clinical study will also be carried out in accordance with national and local regulatory requirement(s).

9.5. Informed Consent

Before each patient is enrolled in the clinical study, written informed consent will be obtained from the patient according to the regulatory and legal requirements of the participating country. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the study treatment in such a manner that the patient is aware of the potential risks, inconveniences, or AEs that may occur. The patient should be informed that he/she is free to withdraw from the study at any time. The patient will receive all information that is required by regulatory authorities and ICH guidelines. The Investigator or designee will provide the Sponsor with a copy of the IRB/IEC-approved ICF prior to the start of the study.

The ICF must be signed and dated; one copy will be given to the patient and the Investigator will retain a copy as part of the clinical study records. The Investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If a protocol amendment is required, then the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the responsible IRB/IEC and signed by all patients subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

9.6. Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). In the United States, following approval, the protocol amendment(s) will be submitted to the IND under which the study is being conducted. Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

9.7. Patient Confidentiality and Data Protection

All clinical study findings and documents will be regarded as confidential. Study documents (protocols, IBs and other material) will be stored appropriately to ensure their confidentiality. The Investigator and members of his/her research team (including the IRB/IEC) must not disclose such information without prior written approval from the Sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial or to comply with regulatory requirements.

The anonymity of participating patients must be maintained. Patients will be specified on study documents by their enrollment number or birth date, not by name. Documents that identify the patient (e.g., the signed informed consent document) must be maintained in confidence by the Investigator.

9.8. Study Monitoring

Monitoring and auditing procedures approved by the Sponsor will be followed in order to comply with GCP guidelines. On-site checking of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal visits from a representative of the sponsor (site monitor) who will review the eCRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and by communications (letter, telephone, and fax).

Major protocol deviations are required to be reported immediately to the Sponsor along with corrective action plans. Based on the information provided by the sites, the Sponsor will provide advice on patient's ability to continue in the study.

All unused study treatment and other study materials will be returned to the Sponsor after the clinical phase of the study has been completed.

9.9. Audits and Inspections

Regulatory authorities, the IRB/IEC, and/or the Sponsor's clinical quality assurance group, or its designee, may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

9.10. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator Brochure, informed consent, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

9.11. Publication Policy

Information regarding publication of study results is contained in the Steering Committee Charter.

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APPENDIX A. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST), V1.1

Response Criteria by RECIST v1.1

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

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

Table 12: RECIST Response for Patients with Measurable Disease: Target Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	> 4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	> 4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once > 4 wks. from baseline**
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.
* See RECIST v1.1 publication [55] for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 13: RECIST Response For Patients with Non-Measurable Disease: Non-Target Disease

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR=complete response; PD=progressive disease.
* Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

APPENDIX B. IMMUNE-RELATED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS

Immune-related RECIST will be used by local site Investigators to assess tumor response and progression and make treatment decisions.

Table 14 provides guidelines for determining objective response incorporating irRECIST. See also details provided in Section 6.3.1.4.

Table 14: Imaging and Treatment after First Radiologic Evidence of Progressive Disease

Tumor Assessment		Confirmation of Response
irCR	Disappearance of all measurable and non-measurable lesions. Lymph nodes must have reduction in short axis to < 10 mm.	Required
irPR	At least 30% decrease in the sum of diameters of measurable lesions, taking as reference the baseline sum diameters.	Required
irSD	Shrinkage does not qualify for irCR/irPR or increase does not qualify for irPD.	Not required
irPD	At least 20% increase and absolute increase of at least 5 mm increase in sum of the diameters of measurable lesions. The appearance of new lesions is not considered PD, but are to be included in the sum diameters.	Confirmation required at least 4 weeks after the first irPD assessment provided the patient is considered clinically stable (see Section 6.3.1.5).

Abbreviations: irCR=immune-related complete response; irPR=immune-related partial response; irSD=immune-related stable disease; irPD=immune-related progressive disease; PD=progressive disease.
Source: Nishino, et al.[56]

APPENDIX C. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Description	Grade
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, i.e., light house work, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4

Source: Oken, et al.[60]

APPENDIX D. COCKCROFT-GAULT FORMULA

A commonly used equation for calculating an estimate of creatinine clearance which estimates glomerular filtration rate (GFR) in ml/min. The formula is:

$$C_{cr} = \frac{(140 - \text{age}) \times \text{weight (in kilograms)} \times [0.85 \text{ if female}]}{72 \times \text{serum creatinine (in mg/dL)}}$$

Source: Cockcroft and Gault [61]

APPENDIX E. SAMPLE EUROPEAN QUALITY OF LIFE SCALE, 5-DIMENSIONS (EQ-5D-5L)

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

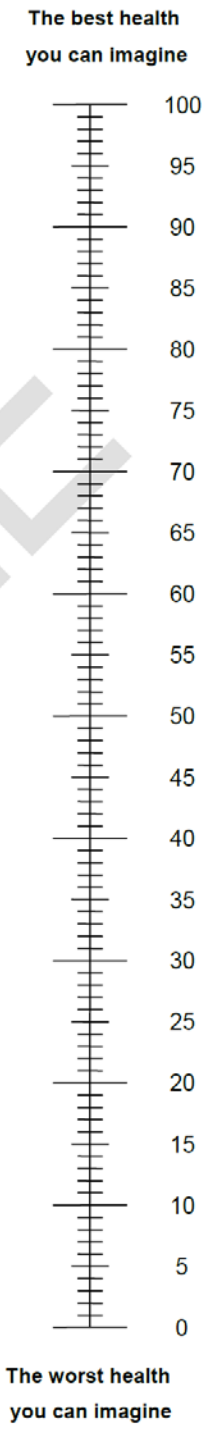
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX F. SAMPLE EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE QUESTIONNAIRE (EORTC QLQ-C30)

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Statistical Analysis Plan (4010-01-001 Part 2B)

Sponsor:	TESARO, Inc.
Protocol No:	4010-01-001 (Part 2B)
PRA Project Id:	TSRTS042-TSR042
Version Date:	08-AUGUST-2019
Version No.:	V2.1

Title:	**A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an anti-PD-1 Monoclonal Antibody, in Patients with Advanced Solid Tumors.**
CRF Version No./Date:	Part 2B/19-DEC-2017
SAP No.	Part 2B v2.1

1.0 Approvals

Sponsor	
Sponsor Name:	TESARO, Inc.
Representative/ Title:	[redacted] Senior Medical Director
Signature /Date:	
Biostatistician/ Title:	[redacted], Senior Director, Biostatistics
Signature /Date:	
PRA	
Project Manager/Title:	[redacted], Project Manager
Signature /Date:	
Biostatistician / Title (Owner):	[redacted], Principal Biostatistician, on behalf of [redacted], Principal Biostatistician *(Original author: [redacted], Sr. Principal Biostatistician)*
Signature /Date:	

Table of Contents

2.0 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses specific to Part 2B of data collected under TESARO Inc. Protocol 4010-01-001 Version 6 (Amendment 5, dated 10-MAY-2019).

3.0 Scope

The SAP is to be developed in two stages. The purpose of using the two stages approach is to develop a SAP so that programming can start earlier in the process. Versions of the SAP up to initial sponsor approval was known as SAP 1. The SAP 1 was drafted well in advance of any study deliverables and maintained throughout the lifecycle of the trial. The SAP for Part 2B will be finalized prior to database lock for Part 2B. This final SAP will require sign off from the PRA Project Manager and TESARO.

The SAP outlines the following:

- Study objectives
- Study design
- Variables analyzed and analysis sets
- Applicable study definitions
- Statistical methods regarding important and significant protocol deviations, study treatment exposure, efficacy analysis, safety analysis (concomitant medications, adverse events handling, laboratory data, and physical examinations), and quality of life analysis

The analysis of pharmacokinetics, pharmacodynamics, anti-drug antibody, and receptor occupancy results will be handled in separate analysis plans.

4.0 Introduction

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol dated 10-MAY-2019 (Version 6) and CRF's dated 19-DEC-2017.

Any further changes to the protocol or CRF may necessitate updates to the SAP.

4.1 Changes from Protocol

Table 12 (RECIST Response for Patients with Measurable Disease: Target Disease) of the protocol states that the minimum requirement for confirmation of CR, PR, and SD should be at least 4 weeks from baseline. In the SAP, this duration has been extended to 12 weeks +/- 10 days to reflect the first tumor assessment after baseline in the Schedule of Events.

5.0 Study Objectives

5.1 Primary Objectives

The primary objectives in the Part 2B Expansion Cohorts is as follows:

- Cohorts A1 and F: To evaluate the antitumor activity of dostarlimab in patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) cancers, including dMMR/MSI-H endometrial cancer (Cohort A1) [redacted]

[redacted], in terms of objective response rate (ORR) and duration of response (DOR) by independent blinded central review using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

- [redacted]
- [redacted]

Where:

- Cohort A1 - Patients with endometrial cancer who have tumors with dMMR by test of IHC or MSI-H (PCR or NGS) and have progressed on or after platinum doublet therapy. Patients have received no more than 2 lines of anti-cancer therapy for recurrent or advanced (Stage ≥IIIB) disease.

[redacted]

5.2 Secondary Objectives

The secondary objectives for Part 2B are as follows:

- To evaluate additional measures of clinical benefit, including:
  - Pharmacokinetic (PK) profile of dostarlimab (This is addressed in a separate SAP)
  - Immunogenicity of dostarlimab (This is addressed in a separate SAP)
  - Immune-related disease control rate (irDCR) based on Investigators' assessment using irRECIST
  - Immune-related duration of response (irDOR) based on Investigators' assessment using irRECIST
  - Immune-related progression-free survival (irPFS) based on Investigators' assessment using irRECIST
  - Progression-free survival (PFS) based on independent blinded central review using RECIST v1.1 (Cohorts A1, [redacted])
  - Immune-related overall response rate (irORR) based on Investigators' assessment using irRECIST (Cohorts A1, [redacted])
  - ORR based on independent blinded central review using RECISTv1.1 in dMMR/MSI-H and Polymerase ε-mutated (POLE-mut) cancers (Cohorts A1 [redacted] Combined)
  - DOR based on independent blinded central review using RECISTv1.1 in dMMR/MSI-H and POLE-mut cancers
  - Disease control rate (DCR) based on Investigators' assessment using RECIST v1.1 (Cohorts A1, [redacted])
  - Overall survival (OS)

5.3 Exploratory Objectives

- To characterize the pharmacodynamic (PDy) profile of dostarlimab
- To explore changes in intratumoral cells and circulating biomarkers in the blood following treatment with dostarlimab
- To explore the profile of tumor-infiltrating lymphocytes (TILs), tumor cell characteristics including genomic alterations (e.g., MMR/MSI and POLE), and/or circulating biomarkers prior to treatment with dostarlimab and correlate with clinical benefit.

- Patient-reported outcomes (PROs) [European Quality of Life scale, 5-Dimensions, 5-Levels (EQ-5D-5L) and European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30)] in patients in Cohorts A1 and F enrolled under Amendment 3 or subsequent amendments (This is addressed in a separate SAP)

6.0 Study Design

This is a multicenter, open-label, first-in-human, Phase 1, dose escalation study with expansion cohorts designed to assess the safety, PK, PDy, and clinical activity of the anti-programmed death-1 (PD-1) antibody, dostarlimab, in patients with advanced solid tumors who have limited available treatment options as determined by the Investigator.

The recommended Phase 2 dose (RP2D) was determined from Part 1 and Part 2A of the protocol, the clinical activity and safety of dostarlimab at the RP2D in selected tumor types will be evaluated in Part 2B.

Figure 1 presents an overview of the planned study schema. The schedule of events for the study are provided in Appendix 6: Immune-Related Adverse Events

Below is a list of MedDRA preferred terms that will be used to identify immune-related adverse events.

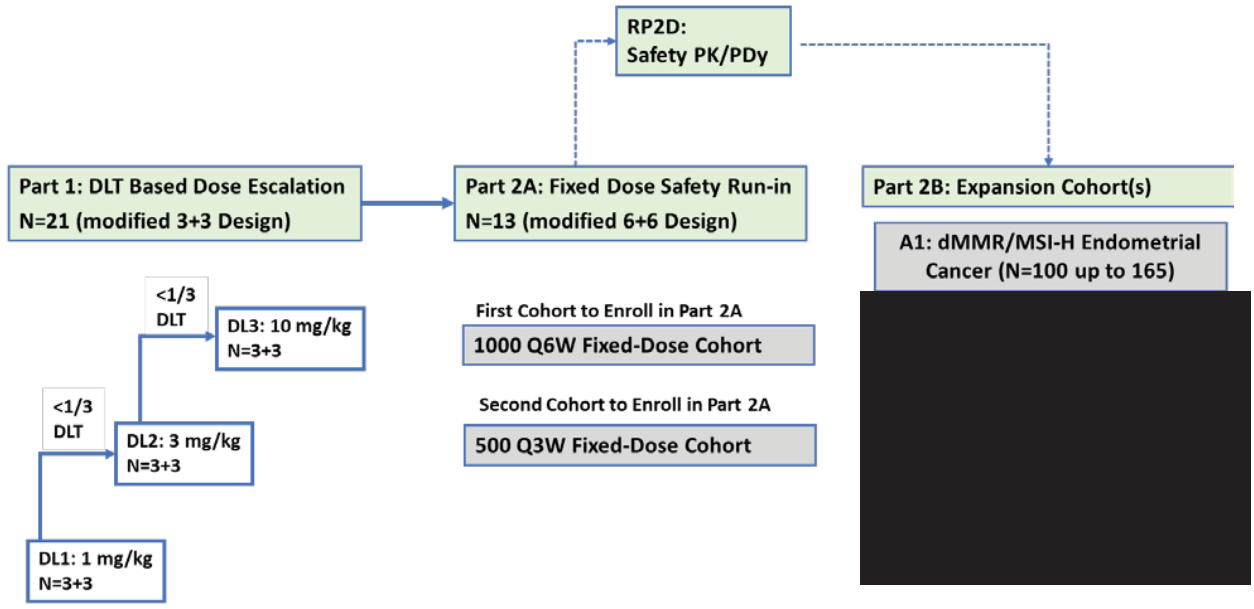
Immune-mediated Pulmonary
Pneumonitis
Sarcoidosis
Immune-mediated Gastro intestinal
Colitis
Diarrhoea
Gastroenteritis
Enteritis
Gastritis
Duodenitis
Immune-mediated hepatic
Autoimmune hepatitis
Hepatitis
Hepatitis toxic
Liver injury
Transaminases increased
Aspartate aminotransferase increased
Alanine aminotransferase increased
Blood bilirubin increased
Hyperbilirubinaemia
Hepatic enzymes increased
Immune-mediated endocrinopathies
Hyperthyroidism
Hypothyroidism
Thyroid disorder
Thyroiditis
Hypophysitis
Hypopituitarism
Adrenal insufficiency
Secondary adrenocortical insufficiency
Type I diabetes mellitus

Diabetic ketoacidosis
Hyperglycaemia
Immune-mediated renal
Nephritis
Renal impairment
Blood creatinine increased
Immune-mediated skin adverse reactions
Rash
Rash maculo-papular
Rash macular
Rash erythematous
Rash papular
Rash pruritic
Rash pustular
Erythema
Exfoliative rash
Dermatitis exfoliative
Autoimmune dermatitis
Pemphigoid
Vitiligo
Pruritus
Steven-Johnson syndrome
Toxic epidermal necrolysis
Immune-mediated pancreatitis
Pancreatitis
Pancreatitis acute
Autoimmune pancreatitis
Amylase increased
Lipase increased
Immune-mediated hematologic
Aplastic anaemia
Autoimmune haemolytic Anaemia
Haemolytic anaemia
Immune-mediated musculo skeletal
Arthralgia
Arthritis
Myositis
Polymyalgia rheumatica
Rhabdomyolysis
Immune-mediated nervous system
Autoimmune neuropathy

Polyneuropathy
Neuropathy peripheral
Peripheral sensory neuropathy
Hypoaesthesia
Paraesthesia
Facial paresis
Dysaesthesia
Demyelination
Myelitis
Encephalitis autoimmune
Seizure
Guillain-Barre syndrome
Motor dysfunction
Myasthenia gravis
Myasthenic syndrome
Immune mediated Ocular
Iridocyclitis
Uveitis
Iritis
Immune mediated cardio vascular
Myocarditis
Vasculitis
Pericarditis
Hypersensitivity
Hypersensitivity
Infusion related reaction
Anaphylactic reaction
Drug hypersensitivity
Type I hypersensitivity
Immune mediated others
Histiocytosis haematophagic
Histiocytosis
Histiocytic necrotising lymphadenitis
Systemic inflammatory response syndrome
Vogt-Koyanagi-Harada syndrome

Appendix 7: Schedule of Events.

Figure 1: Study Schema



Abbreviations: DL=dose level; DLT=dose limiting toxicity; dMMR=mismatch repair deficient; MSI-H=microsatellite instability high; MSS=microsatellite stable; [redacted]; N =number (of patients); MMR-p=mismatch repair proficient, POLE-mut= polymerase ε mutated; RP2D=recommended Phase 2 dose;

6.1 Randomization

Not applicable, as all patients receive active treatment.

6.2 Sample Size Consideration

Sample size calculations were performed using SAS® version 9.4.

For Part 2B, a total sample size of up to 680 patients is estimated for the expansion portion of this study to provide assessment of clinical activity of dostarlimab based on ORR.

Cohort A1 will enroll approximately 100 with the potential for up to 165 patients with dMMR/MSI-H EC, [redacted] Adjustments to enrollment within cohorts may occur based on emerging data and Sponsors decision.

For Cohort A1 in Part 2B, the null hypothesis that the true response rate is ≤20% (H0: $p \leq 0.2$) will be tested against a one-sided alternative of ≥40% (Ha: $p \geq 0.4$). With 65 subjects treated, the cohort has 92% power to rule out a ≤ 20% ORR (null hypothesis) when the true ORR is 40% at the 2.5% type I error rate (one-sided). Of note, given a recent report where 6 of 9 patients with MSI endometrial cancer achieved a clinical response following treatment with an anti-PD-1 antibody, the activity of dostarlimab in this patient population is expected to negate the necessity for a two-stage design and thus there will not be an interim analysis in this cohort.

The sample size of Cohort A1 will be increased to 100 patients which will allow the lower-limit boundary of the exact 95% confidence interval excluding a response rate of 25% or less and assuming observed ORR is 35%.

[redacted]

[redacted]

7.0 Study Variables and Covariates

7.1 Primary Variables

7.1.1 Primary Safety Variables

- Treatment-emergent AEs (TEAEs): All, serious adverse events (SAEs), relationship to study treatment and intensity (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] severity grades)
- TEAEs leading to discontinuation
- TEAEs leading to death
- Immune-related adverse events (irAEs) of interest
- Clinical laboratory measures: hematology, chemistry, coagulation, thyroid function, urinalysis
- Vital signs
- Electrocardiogram (ECG)
- Physical examination
- Eastern Cooperative Oncology Group (ECOG) status
- Serum pregnancy testing
- Concomitant medications

7.1.2 Primary Efficacy Variables

- Cohorts A1, A2 and F: ORR and DOR for dostarlimab using RECIST v 1.1 based on blinded central review

- Cohort E: irORR for dostarlimab using irRECIST based on Investigator assessment

7.2 Secondary Variables

7.2.1 **Secondary Efficacy Variables**

- irDCR using irRECIST
- irDOR using irRECIST
- irPFS using irRECIST
- PFS based on independent blinded central review using RECIST v 1.1 (Cohorts A1, [redacted])
- irORR for Cohorts A1, [redacted] based on Investigator assessment using irRECIST
- DOR based on independent blinded central review using RECIST v1.1 in MSI-H and POLE-mut cancers (Cohorts A1, [redacted])
- DCR based on independent blinded central review using RECIST v1.1 (Cohorts A1, [redacted])
- OS
- PRO Endpoints: EQ-5D-5L and EORTC QLQ-C30 in Cohorts A1 and [redacted] (addressed in a separate SAP)

7.3 Exploratory Variables

- Circulating biomarkers at baseline
- Change from baseline in circulating biomarkers. Biomarkers may include
  - serum cytokines
  - gene expression of circulating immune cells
  - circulating tumor cells
  - circulating tumor DNA

Genomic alterations (e.g. MSI and POLE)

- The profile of TILs
- The profile of tumor cell characteristics

8.0 **Definitions**

8.1 General

Age
The age collected at time of screening, presented in whole years as collected.

Age Group
There will be three age groups summarized in the demographics tables: <65 years old, ≥65-75 years old and ≥75 years old based on age at time of screening.

Baseline
Unless otherwise specified, baseline is the last measurement taken on or prior to first dose of dostarlimab (baseline can be the same date as first dose, given the measurement is expected prior to first dose, otherwise consider both time and date of dosing [if time is available for both]).

Body Mass Index (BMI):
Calculated at each visit and is equal to the weight (in kg)/ [height at screening (in $m)^2$].

Change from Baseline
Change from baseline is defined as (value at post-baseline visit – baseline value [as defined above]).

Month:
A time period in months will be calculated as (12/365.25)*(number of days of interest in the period).

Post-baseline Visit
All visits occurring from the first post-baseline visit until the last visit at the end of study, including unscheduled visits.

Study Treatment
The study treatment is defined as dostarlimab (TSR-042).

8.2 Exposure

Exposure parameters will be summarized as noted in Table 1 below.

Table 1: Study Treatment Parameters by Study Phase

Parameter	Phase 2B
Dosing schedule per protocol	500mg Q3W (first 4 cycles), followed by 1,000mg Q6W for all subsequent cycles beginning on Day 1/Cycle 5
Intended dose (mg/day)	(mg/day) First 4 Cycles: 500/21 After Cycle 5: 1000/42
Duration of Treatment (day)	Overall: If the last cycle of the treatment is <=4 cycles, Last dose date – Start dose date + 21 If the last cycle of the treatment is >=5 cycles, Last dose date – Start dose date + 42 First 4 cycles: Last dose date prior to cycle 5 – Start dose date + 21 After cycle 5: Last dose date – First Dose Date at or after Cycle 5 + 42
Actual Cumulative Dose (mg)	Sum of the doses (mg) administered Calculated separately for the first 4 cycles and cycles after cycle 5
Actual Dose intensity (ADI) (mg/day)	Actual Cumulative Dose/Duration of Treatment Calculated separately for the first 4 cycles and cycles after cycle 5
Relative Dose Intensity (%)	Actual Dose Intensity/Intended Dose Calculated separately for the first 4 cycles and cycles at or after cycle 5

8.3 Safety

Immune related adverse events of interest (irAE)

irAEs are identified as any >=Grade 2 AEs based on a pre-specified search list of preferred terms (PTs), documented in a version-controlled repository maintained by TESARO and finalized for analysis of the current study data prior to DB lock. This list is presented in Appendix 6.

Treatment Emergent Adverse Event (TEAE)
TEAEs are defined per protocol as any AE or SAE with onset beginning at the day of first administration of study treatment, throughout the treatment period until 90 days after end of treatment (EOT) visit (or until the start of alternate anticancer therapy, whichever occurs earlier), or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study. An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dose date of either study treatment, will be considered to be treatment emergent.

Treatment Period
The period from the date of first dose of any study medication up to and including 90 days after the end of EOT visit or the earliest date of subsequent anticancer drug therapy, whichever occurs first, unless otherwise stated.

TEAEs Related to Study Treatment

Any TEAE assessed by the Investigator as related to study treatment ('Related', 'Possibly Related', or missing)

Study phases:

Phases of the study are defined as follows:

- **Prior to treatment period**: Prior to first dose of dostarlimab
- **Active treatment period**:
  - If the last cycle of dostarlimab treatment is ≤4 cycles, active treatment period is calculated from the date of first dose to date of last dose of dostarlimab + 21 days;
  - If >4 cycles of dostarlimab are received, the active treatment period is calculated from the date of first dose to date of last dose of dostarlimab + 42 days
- **90-day safety follow up period**: Within 90 days after EOT visit of dostarlimab and first follow-up anti-cancer therapy, whichever is earlier
- **Long term follow up period**: After EOT VISIT of dostarlimab + 90 days or first follow-up anti-cancer therapy, whichever is earlier.

8.4 Efficacy

Best Overall Response (BOR and irBOR)

- Per RECIST (v 1.1): The best overall response (BOR) according to RECIST v 1.1 [Appendix 4; [3]] will be programmatically derived based on reported timepoint response assessments as determined by a central reader (cohorts A1, A2 and F) according to RECIST v1.1, at different evaluation timepoints from the first dose date until the first documented disease progression.

  BOR for patients in cohorts A1, A2, and F is determined according to the following rules:

  - Complete Response (CR) = at least two consecutive determinations of CR more than 4 weeks apart with no other assessment between the two determinations other than unable to evaluate (NE), CR or missing.

- Partial Response (PR) = at least two consecutive determinations of PR or better more than 4 weeks apart with no other assessment between the two determinations other than NE, CR, PR or missing before progression (and not qualifying for a CR).
- Stable Disease (SD) = at least one SD or NN (Non-CR/Non-PD) assessment (or better) ≥ 12 weeks - 10 days (≥ 74 days) after baseline and before progression (and not qualifying for a CR or PR). For an unconfirmed PR or CR to qualify, it must still meet 12 week -10 days requirement.
- Progressive Disease (PD) = progression after baseline. Note that a determination of CR followed at least 4 weeks later by an SD will result in a BOR of PD.
- No Disease (ND) = For central imaging data, when the independent radiologist cannot identify any disease at baseline, all subsequent assessments will be ND, if not declared PD or NE.

Clinical deterioration will not be considered as documented disease progression. Only tumor assessments performed before or on the start of any new anti-cancer treatment (including radiation therapy to the tumor lesion (s)) will be considered in the assessment of BOR.

- Per irRECIST: The immune-related BOR (irBOR) according to irRECIST [Appendix 4] will be programmatically derived based on reported overall timepoint responses as determined by Investigators based on assessment of radiological scans according to irRECIST, at different evaluation timepoints from the first dose date until documented disease progression. irBOR is determined according to the following rules:
  - Immune-related Complete Response (irCR) = at least two consecutive determinations of irCR at least 4 weeks apart with no evidence of progression between the two determinations other than unable to evaluate (NE), irCR or missing.
  - Immune-related Partial Response (irPR) = at least two consecutive determinations of irPR or better at least 4 weeks apart with no evidence of progression between the two determinations other than unable to evaluate (NE), irPR or missing (and not qualifying for irCR).
  - Immune-related Stable Disease (irSD) = at least one irSD assessment (or better) ≥ 12 weeks -10 days (≥74 days) after baseline (and not qualifying for an irCR or irPR). Unconfirmed irPR and irCR will be categorized as irSD if it was done 12 weeks – 10 days after the first dose.
  - Immune-related Progressive Disease (irPD) = progression after baseline not qualifying for an irCR/irPR/irSD without any further tumor assessment before treatment discontinuation. Note that a determination of irCR followed at least 4 weeks later by an irSD will result in an irBOR of irPD.

  Clinical deterioration will not be considered as documented disease progression. Only tumor assessments performed before or on the start of any new anti-cancer treatment (including radiation therapy to the tumor lesion (s)) will be considered in the assessment of irBOR.

Disease Control Rate (DCR and irDCR)

- Per RECIST (v1.1): DCR is defined as the proportion of patients achieving BOR of confirmed CR, PR, or SD.
- Per irRECIST: irDCR is the proportion of patients achieving irBOR of irCR, irPR, or irSD as assessed by the Investigator.

Duration of Response (DOR and irDOR)

- Per RECIST (v1.1): Duration of response is defined as the time from first documentation of overall response leading to a confirmed CR or PR when confirmation is required in cohorts A1, A2 and F by RECIST v1.1 until the time of first documentation of overall response of disease progression or death.
- Per irRECIST: Duration of response is defined as the time from first documentation of timepoint response leading to a confirmed irCR or irPR until the time of the irPD event or death.

Clinical deterioration will not be considered as documented disease progression. Only tumor assessments performed before or on the start of any new anti-cancer treatment (including radiation therapy to the tumor lesion (s)) will be considered in the assessment of DOR and irDOR.

irPD event

To account for initial tumor flare after immune-oncological treatment, progression for irRECIST will be considered when any of the following occurs:

- Two consecutive irPDs are observed, the first irPD will be considered the date of the irPD event
- The only or last tumor assessment prior to treatment discontinuation is irPD, this will be considered the date of the irPD event

Last Known Contact Date:

The date of last known contact will be derived for patients at the analysis cutoff using the latest complete date among the following:

- Patient assessment dates (blood draws [laboratory, PK], vital signs, ECOG performance status, ECG, tumor assessments, tumor measurement, or tumor biopsy dates)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation.
- AE start and end dates
- Concomitant medication start and end dates
- Concurrent procedure date
- Date of death collected on the 'Discontinuation of Study' electronic Case Report Form (eCRF).
- Date of last contact collected on the survival follow-up eCRF where status is 'alive'.
- Study treatment start and end dates.
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up).

Only dates associated with actual contact of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed will not be used. Assessment dates after the cutoff date will not be applied to derive the last contact date, if applicable

Objective Response Rate (ORR and irORR)

- Per RECIST (v1.1): The ORR is the proportion of patients who achieved BOR of CR or PR per RECIST v1.1.

- Per irRECIST: The irORR is defined as the proportion of patients who achieved irBOR of irCR or irPR per irRECIST.

Patients who do not have a post-baseline radiographic tumor assessment, who receive post baseline anti-tumor treatments (including surgery or radiation to the tumor lesions) other than the study treatments prior to reaching a CR/irCR or PR/irPR, or who die, progress, or drop out for any reason prior to reaching a CR/irCR or PR/irPR will be counted as non-responders in the assessment of ORR/irORR.

Overall Survival (OS)
An OS time is defined as the time from date of first dose of study treatment to the date of death by any cause. Patients last known to be alive will be censored at date of last known contact.

OS(days)=Date of Death/Censoring – Date of First Dose +1

Progression-Free Survival (PFS)

- Per RECIST (v1.1): A PFS time is defined as the time from date of first dose to the earlier date of assessment of progression or death by any cause in the absence of progression based on the time of first documentation of PD per RECIST v1.1
- Per irRECIST: An irPFS time is defined as the time from date of first dose to the earlier date of assessment of irPD event or death by any cause in the absence of progression based on the time of irPD event per irRECIST.

  PFS(days)=Date of <PD or irPD event or death> / Censoring – Date of First Dose +1

  Only tumor assessments performed before the start of any new anti-cancer treatment (including radiation therapy to the tumor lesion (s)) will be considered in the assessment of PFS/irPFS.

9.0 Analysis Sets

9.1 Screening Analysis Set

All patients who signed the informed consent form including screen failures.

9.2 Safety Analysis Set

All patients who receive any amount of study drug.

9.3 Efficacy Analysis Set

Primary efficacy analysis set (RECIST 1.1 per BICR): All patients in Safety Analysis Set with measurable disease at baseline (defined at the existence of at least one target lesion at baseline tumor assessment by BICR) who have had the opportunity for at least 24 weeks of tumor assessment at the time of analysis.

Secondary efficacy analysis Set (irRECIST 1.1 per Investigator assessment): All patients in Safety Analysis Set with measurable disease at baseline (defined at the existence of at least one target lesion at baseline tumor assessment by Investigator) who have had the opportunity for at least 24 weeks of tumor assessment at the time of analysis.

10.0 Patients Allocation

All analyses (demographic, baseline characteristics, safety and efficacy) will be performed for each tumor type separately based on testing performed and recorded in the CRF, as indicated in Appendix 7.

- Endometrial patients: Cohorts A1 and A2
  - results will be presented by MMR status (dMMR, MMRp and MMR unknown) as per the results of the available MMR IHC test.
  - Subjects with known MMR status will be summarized under that status regardless of MSI-H/MSS status i.e. dMMR/MMRp columns include both MSI-H and MSS subjects.

dMMR or (MMR-unk & MSI-H) EC			MMRp or (MMR-unk & MSS) EC			All EC
dMMR (n=a)	MMR-unk/MSI-H (n=b)	Total (n=a+b)	MMRp (n=x)	MMR-unk/MSS (n=y)	Total (n=x+y)	Overall (n=a+b+x+y)

- [redacted]

- [redacted]

11.0 Interim Analyses

There will be 1 planned interim analysis for dMMR patients from Cohort A1 and Cohort F combined for administrative purposes. The interim analysis will occur when approximately 100 dMMR patients enrolled from Cohorts A1 and F combined and have been followed for at least 6 months.

The interim analysis will be based on confirmed response per RECIST 1.1 using BICR.

12.0 Data Review

Final data for analysis will be cleaned prior to receipt by statistical programming. Ongoing data handling will take place by the study programmer, until the time at which the study team has full access to the data.

12.1 Data Handling and Transfer

All data will come from third party vendors via the TESARO data management group to PRA. PRA will extract data in SAS® dataset format (SAS v9.4 or higher) directly from the RAVE clinical database system and convert the data to SDTM v3.2 or higher. ADaM Implementation Guide v1.1 will be followed. Please refer to the TESARO documentation of the Data Management Plan for further details of this process.

12.2 Data Cleaning

PRA will be programming analysis datasets and tables, figures, and listings (TFLs). Data issues identified during the process of programming analysis datasets and TFLs will be sent to TESARO data management.

All derived datasets will include patient-level variables, such as analysis set inclusion, sex, tumor cohort, and dose dates.

Any methodologies used to address any issues identified in the data will be documented in the analysis data set specifications and finalized before database lock.

Variables generated at the patient level will be stored in a consolidated data set for the study. Variables at the patient level or below (e.g., at the visit level) will be generated in analysis data set programs, not in the programs generating the TFLs. Exceptions may include simple concatenation or formatting that will only be used once.

The content of the analysis data sets will be detailed in a separate document. For each derived data set, the label, sort order, and structure (expected number of records per patient/visit) will be specified. For each variable, the name, label, type, length, format, and source or derivation description will be specified. Detailed rules devised to handle specific data patterns found in data reviews will be included. The analysis dataset specifications will be finalized before database lock.

Review of a pre-lock TFL run on the ready-to-lock database allows identification of data issues prior to lock. The pre-lock TFLs may be discussed with TESARO in a data review meeting to identify any final data issues and seek corrections prior to database lock. The PRA statistician and TESARO must approve database lock ahead of locking the database

12.3 Handling of Dropouts and Missing Data

Missing observations will generally be treated as missing at random and will not be imputed, unless otherwise noted.

Note, for all listings the actual value for date (not imputed) will be presented in all data listings and imputed dates calculated as follows will only be used for programming flags, etc.

Incomplete dates for disease history (e.g. initial diagnosis date; date of documented, locally advanced, metastatic disease diagnosis; date of treatment initiation) will be imputed as follows:

- If the day is missing, it will be imputed to the 1st day of the month.
- If both day and month are missing, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

Incomplete dates for progression in prior treatment will be imputed as follows:

1. If progression date is partial missing day only, use imputed progression date (imputing missing day = 15th)

2. If progression date is partial missing both day and month, do the following:
    a. if next regimen start date is not missing/partial AND year(next regimen start date) = year of progression, progression date= next regimen start date
    b. if next regimen start date is not missing/partial, and year(next regimen start date) > year of progression, progression date= 15 Dec (year of progression)
3. Else if progression date = missing and next regimen start date is not missing/partial, PD date= Next regimen start date
4. Else, progression date = current regimen end date

Incomplete dates for adverse event and concomitant medication dates will be imputed as follows:

Start Date:

- If only 'day' is missing, and the month and year are not the same as the month and year of first dose, then impute day with '01'. Otherwise, if the month and year are the same as first dose date, use first dose date.
- If 'day' and 'month' are missing, and 'year' is not missing, then impute month and day with month and day of first dose date (assuming same 'year').
- If the year is not the same as the year of first dose, impute 01 for day and 01 for month.
- If the start date is completely missing, it will be set to the first dose date.

Stop Date:

- If only 'day' is missing, impute day with last day of the month.
- If 'day' and 'month' are missing, and 'year' is not missing, then impute month with '12' and day with '31' (or date of study discontinuation/completion if earlier than 12-31).
- If the stop date is completely missing, it will be set to the date of study discontinuation/completion. A stop date will not be applied to ongoing AEs.
- If the imputed stop date is greater than last contact date then set to last contact date.

Incomplete start date of follow-up anti-cancer treatment will be imputed as follows:

- If only 'day' is missing, then impute day with last day of the month.
- If 'day' and 'month' are missing, and 'year' is not missing or the same as the year of last dose, then impute as December 31st.
- If the imputed start date is greater than last contact date then set to last contact date.

13.0 Statistical Methods

In general, categorical data will be summarized using number of patients (n), frequency and percentages, with the denominator for percentages being the number of patients in the analysis set for each cohort. Percentages will be rounded to 1 decimal place except for 100%, which will have no decimal place. Two-sided exact 95% confidence intervals (CIs) based on the Clopper-Pearson method [(2)] will be provided to summarize the binomial proportion of the ORR/irORR and DCR/irDCR for both RECISTv1.1 and irRECIST assessments where applicable

Continuous data will be summarized using the number of patients, mean, standard deviation, median, first and third quartiles (Q1, Q3), minimum, and maximum. The mean, median, Q1 and Q3 will be presented to 1 decimal place greater than the original data; the standard deviation will be presented to 2 decimal places greater than the original data; and the minimum and maximum will have the same number of decimal places as the original data.

Time-to-event analyses will be performed using Kaplan-Meier (KM) methods.

All statistical analyses and data listings will be performed using SAS v9.4 or higher.

13.1 Patient Disposition

Disposition of patients includes the number and percentage of patients for the following categories:

- patients in each of the analysis sets,
- patients discontinued from treatment,
- primary reason for discontinuation from treatment,
- patients discontinued from the study, and
- primary reason for discontinuation from the study.
- Patients who were treated beyond initial disease progression
- Patients died while on study, and
- Primary reason for death while on Study

Treated beyond initial disease progression is defined as: last dose of study drug > first instance of irPD (irRECIST)

Died while on study is defined as: death occurring after informed consent and before EOS visit

A listing will present data for patient disposition.

13.2 Important and Significant Protocol Deviations

Important and Significant Protocol Deviations (ISPDs) will come from PDMS (clinical database) and CTMS. The IPSD categories include, but are not limited to:

Important Deviations

A protocol deviation is classified as an important PD if there is the potential to:

- Failure to obtain informed consent for participation in the clinical trial
- Enrollment of an ineligible subject
- Subject developed withdrawal criteria during the study but was not withdrawn
- Subject received incorrect treatment
- Incorrect or non-compliant dosing of a subject, i.e. dosing that is inconsistent with the protocol
- Administration of an excluded concomitant treatment to a trial subject
- Impact the completeness, accuracy, and/or reliability of the study data, or
- Affect a subject's rights, safety, or well-being.

Significant Deviations

A protocol deviation is classified as a significant PD if it has been confirmed to:

- Adversely impact the completeness, accuracy, and/or reliability of the study data
- Affect a subject's rights, safety, or well-being

The TESARO MM reviews, assesses, and classifies PDs in consultation, as needed, with Pharmacovigilance, the Biostatistician, the CTM, and as appropriate, Clinical Pharmacology and/or

other Study Team members throughout the clinical trial at intervals defined in the Medical Data Review Plan (MDRP).

Important and significant categories will be summarized. A listing of ISPDs including deviation visit, deviation type, deviation description, and any relevant comments will be generated.

13.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Safety Analysis set and Primary Efficacy Analysis set using descriptive statistics. No formal statistical comparisons will be performed.

Descriptive statistics will be provided for age (<65, ≥65 to <75, and ≥75), sex (male vs. female), race (American Indian or Alaska Native, Asian, Black, Native Hawaiian or other Pacific Islander, White, or other), Ethnicity (Hispanic or Latino or Non-Hispanic or Latino), and baseline values for weight (kg), height (m), and BMI (kg/m^2).

Demographic, baseline characteristics, and medical history data for each patient will be provided in data listings.

13.3.1 **Primary Cancer History**

A summary of primary cancer history will be presented for the Safety Analysis set and Primary Efficacy Analysis set including: the primary tumor site, histologic diagnosis, distant metastasis, grade of disease at diagnosis, tumor status, the presence of certain biomarker expressions and stage at diagnosis, where applicable.

Listings for cancer histories will be presented and include: the overall cancer stage at first diagnosis, the primary tumor, regional lymph node, the distant metastasis, histology at diagnosis, grade of disease at diagnosis, most recent overall cancer stage most recent primary tumor, most recent regional lymph node, most recent distant metastasis, and the presence of certain gene mutations and translocations.

13.3.2 **Medical History, Surgical History**

General medical history information (including past and ongoing) and prior medications will be summarized for category and conditions ongoing or resolved at study entry for the Safety Analysis set and Primary Efficacy Analysis set. Medical history conditions will be collected at time of screening. The count and percentage of patients with each medical history event will be summarized by categories and described conditions. General medical history information will be coded by System Organ Class (SOC) and PT using MedDRA, using the most recent version available at the data cutoff. The count and percentage of patients with each medical history event will be summarized by MedDRA SOC and PT for all patients. SOCs will be presented by descending frequency with PTs in descending order of frequency for medical history within the SOC (and further sorted alphabetically, for PTs with the same number of AEs reported within a SOC).

A by-patient listing of general medical history will be provided by patient ID number in ascending order.

Prior anticancer treatment will be summarized by regimen for all patients in the Safety Analysis set.

Prior anti-cancer regimens, along with prior response information will be listed.

Prior surgery and radiotherapy performed prior to informed consent will also be listed.

The number and percentage of patients in each of the following prior anti-cancer therapy categories will be tabulated:

- Patients with at least one type of prior anti-cancer treatment (including surgery, radiotherapy or drug therapy)
- Patients with at least one prior anti-cancer radiotherapy
- Patients with at least one prior anti-cancer surgery

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of patients with the following:

- Patients with at least one prior anti-cancer drug therapy
- Number of any prior anti-cancer therapy regimens: 0, 1, 2, 3, ≥4

Number of prior lines of anticancer treatment for metastatic disease: includes prior anticancer regimens that were given for metastatic disease excluding hormonal therapy as single agent treatment (i.e. Agents excluded – MEGESTROL, MEGESTROL ACETATE, ANASTROZOLE, LETROZOLE, SILYBUM MARIANUM EXTRACT, MEDROXYPROGESTERONE ACETATE, TAMOXIFEN, GOSERELIN): 0, 1, 2, 3 ≥4

- Prior bevacizumab use: Yes vs. No
- Best overall response from the last platinum-containing prior anti-cancer therapy, as recorded in the CRF
- Progression free interval from the last platinum-containing prior anti-cancer therapy, calculated in days as (date of progression – last platinum-containing prior anti-cancer therapy date of treatment start) + 1, then multiplied by the conversion factor 12/365.25 to present in months.

13.4 Treatments

13.4.1 **Extent of Study Treatment Exposure**

Study treatment is dostarlimab administered through 30-minute infusions. Refer to Appendix 6: Immune-Related Adverse Events

Below is a list of MedDRA preferred terms that will be used to identify immune-related adverse events.

Immune-mediated Pulmonary
Pneumonitis
Sarcoidosis
Immune-mediated Gastro intestinal
Colitis
Diarrhoea
Gastroenteritis
Enteritis
Gastritis
Duodenitis

Immune-mediated hepatic
Autoimmune hepatitis
Hepatitis
Hepatitis toxic
Liver injury
Transaminases increased
Aspartate aminotransferase increased
Alanine aminotransferase increased
Blood bilirubin increased
Hyperbilirubinaemia
Hepatic enzymes increased
Immune-mediated endocrinopathies
Hyperthyroidism
Hypothyroidism
Thyroid disorder
Thyroiditis
Hypophysitis
Hypopituitarism
Adrenal insufficiency
Secondary adrenocortical insufficiency
Type I diabetes mellitus
Diabetic ketoacidosis
Hyperglycaemia
Immune-mediated renal
Nephritis
Renal impairment
Blood creatinine increased
Immune-mediated skin adverse reactions
Rash
Rash maculo-papular
Rash macular
Rash erythematous
Rash papular
Rash pruritic
Rash pustular
Erythema
Exfoliative rash
Dermatitis exfoliative
Autoimmune dermatitis
Pemphigoid
Vitiligo

Pruritus
Steven-Johnson syndrome
Toxic epidermal necrolysis
Immune-mediated pancreatitis
Pancreatitis
Pancreatitis acute
Autoimmune pancreatitis
Amylase increased
Lipase increased
Immune-mediated hematologic
Aplastic anaemia
Autoimmune haemolytic Anaemia
Haemolytic anaemia
Immune-mediated musculo skeletal
Arthralgia
Arthritis
Myositis
Polymyalgia rheumatica
Rhabdomyolysis
Immune-mediated nervous system
Autoimmune neuropathy
Polyneuropathy
Neuropathy peripheral
Peripheral sensory neuropathy
Hypoaesthesia
Paraesthesia
Facial paresis
Dysaesthesia
Demyelination
Myelitis
Encephalitis autoimmune
Seizure
Guillain-Barre syndrome
Motor dysfunction
Myasthenia gravis
Myasthenic syndrome
Immune mediated Ocular
Iridocyclitis
Uveitis
Iritis
Immune mediated cardio vascular

Myocarditis
Vasculitis
Pericarditis
Hypersensitivity
Hypersensitivity
Infusion related reaction
Anaphylactic reaction
Drug hypersensitivity
Type I hypersensitivity
Immune mediated others
Histiocytosis haematophagic
Histiocytosis
Histiocytic necrotising lymphadenitis
Systemic inflammatory response syndrome
Vogt-Koyanagi-Harada syndrome

Appendix 7: Schedule of Events for a detailed schedule of infusion in Part 2B.

A summary of study treatment exposure will be presented for the Safety Analysis set and will include the following.

- Actual duration of exposure (days)
- Cumulative dose and total number of doses administered
- The actual dose intensity
- Relative dose intensity
- The number and percentage of patients with
    - infusion delays
    - infusion interruptions
    - at least one reported missed infusion

Swimmer plots for all patients will be produced and will depict each patient's duration of exposure as a separate bar (horizontally) over time.

A by-patient listing based on the safety population will also be produced.

13.4.2 Prior and Concomitant Medications

Medications collected at Screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary (version WHODrug-DDE-B2\201709). The medications will be categorized as prior or concomitant using the following definitions:

- Prior medications: any medications which started and ended prior to the first dose date of study treatment.
- Concomitant medications: any medications, other than study treatments, starting prior to first dose and ongoing at first dose, being taken on or after the initial study treatment dosing date, through 90 days after the last dose or until the start of subsequent antitumor therapy

Both prior medications and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC level 3) classification drug class and WHO preferred name using the number and percentage of patients for each cohort. A patient reporting the same medication more than once will be counted only once when calculating the number and percentage of patients who received that medication in a given time category (prior or concomitant). The summary of prior and concomitant medications will be ordered by descending frequency with respect to drug class and then by descending frequency of preferred name in total within the drug class. For drugs with the same frequency, sorting will be done alphabetically. Summaries will be based on the safety population.

All prior and concomitant medications will be provided in a by-patient listing sorted by patient ID number and administration date in chronological order.

13.5 Safety Analyses

Safety Tables and Listings will be presented to summarize TEAEs, laboratory data, and vital signs overall and by cohort. The Safety analysis set will be used, unless noted otherwise.

In general, all by visit summaries of safety parameters will only be summarized up to and including month 6 and at the treatment discontinuation visit. Additional summaries will be derived as the minimum and maximum for all on-study assessments and presented similarly to the other time points at the end of the summary table. This will allow an assessment of either the best or worst value assessed throughout the conduct of the study. The maximum and minimum calculations will use all post-baseline data, including any unscheduled assessments.

In general, unscheduled measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in assessing the minimum and maximum of all visits and in the analysis of notable post-baseline results (for example notable abnormal ECG results).

13.5.1 **Adverse Events**

Adverse events will be coded using the MedDRA. Only TEAEs (refer to Section 8.3 for definition for this study) will be analyzed but all AEs occurring on-study will be listed in patient data listings.

An overall summary TEAE table will include numbers and percentages of patients who had:

- at least one TEAE,
- TEAEs related to study treatment,
- CTCAE Grade 3 or higher TEAEs,
- CTCAE Grade 3 or higher TEAEs related to study treatment,
- SAEs
- SAEs related to study treatment,
- TEAEs resulting in treatment discontinuation,
- TEAE’s resulting in study drug infusion interruption,
- TEAE’s resulting in study drug treatment interruption,
- Immune-related AEs of interest,
- Treatment-related AEs leading to discontinuation of study treatment,
- Treatment-related AE with outcome of Death
- TEAE leading to Death

AEs will be tabulated by SOC and PT. Patients with the same AE more than once will have that event counted only once within each SOC, and once within each PT. By-patient listings of immune-related AEs of interest will be presented if appropriate.

Summary tabulations include the following subsets:

- Incidence of patients with any AE assessed by the Investigator as related to study treatment.
- Incidence of TEAEs.
- Incidence of treatment related TEAE
- Incidence of irAE
- Incidence of TEAEs resulting in discontinuation of study treatment
    - A by-patient listing of TEAEs resulting in discontinuation of study treatment will be presented.
- Incidence of treatment-related TEAE resulting in discontinuation of study treatment
- Incidence of TEAEs resulting in infusion interruptions.
- Incidence of TEAEs resulting in treatment interruptions.
- Incidence of CTCAE Grade 3 or greater TEAEs. Patients with the same TEAE with more than one grade will be counted under the maximum grade within each SOC, and once within each PT.
- Incidence of Treatment-related CTCAE Grade 3 or greater TEAEs. Patients with the same TEAE with more than one grade will be counted under the maximum grade within each SOC, and once within each PT.
- Most commonly reported (at least 5% of all patients) treatment-emergent and treatment related TEAEs.

13.5.1.1 Subgroup Analysis

Subgroup analysis of TEAE and treatment-related TEAE will be performed for each of the following subgoups

- # of prior therapy: (1 vs. ≥2)
- Prior Radiation: (Yes vs. No)
- Prior Bevacizumab use: (Yes vs. No)

13.5.2 **Deaths and Serious Adverse Events**

The following will be presented (regardless of treatment-emergent AE status) by cohort:

- Number and percentage of patients experiencing the following while on-treatment (regardless of onset date, present between first study treatment dose and 90 days after last dose), summarized by MedDRA SOC and PT:
    - At least 1 SAE
    - Treatment-related SAEs
    - A by-patient listing of all SAEs will be presented.
- Incidence of deaths while patients are on-study.
    - Deaths during the active treatment period, during 90-day safety follow-up period and during long-term follow-up period
    - TEAEs leading to death by AE PT
    - Cause of death
    - A by-patient listing of deaths (including days since last dose) will be presented.

13.5.3 Laboratory Data

Laboratory data will be summarized both as continuous data and by severity. Multiple measurements taken during the visit for a patient will be represented by the most severe value for each test. The most severe value will be determined first by the value closest to the upper or lower limit of the normal limits (dependent on which direction is considered more severe) if the value is within the normal limits. If the value is outside the normal limits, the value furthest from the upper or lower limit will be selected (dependent on which direction is considered more severe). In the event that this algorithm does not allow for determining the most severe (i.e. a tie), the measurement closest to dosing date will be selected.

For continuous data, the following hematology tests will be summarized:

- WBC count, lymphocytes, monocytes, absolute neutrophil count, eosinophils, basophils, hemoglobin, platelets, mean platelet volume, mean corpuscular volume.

The following chemistry tests will be summarized:

- Sodium, amylase, potassium, total bilirubin, corrected calcium, alkaline phosphatase (ALP), magnesium, aspartate aminotransferase (AST), chloride, glucose, alanine aminotransferase (ALT), total protein, creatinine, albumin, urea or blood urea nitrogen, lactate dehydrogenase.

The following coagulation factors will be summarized: International normalized ratio (INR) and activated partial thromboplastin time (aPTT).

The following urinalysis parameters will be summarized:

- Specific gravity, protein, leukocyte esterase, glucose, nitrite, ketones, blood,

Additionally, a by-patient listing will be presented for thyroid functions (thyroid-stimulating hormone, triiodothyrone (T3), or free T3 and free thyroxin), serum CA-125 (ovarian cancer [OC] patients).

NCI CTCAE v 4.03 grades will be applied for the following lab parameters:

- Hematology: hemoglobin (anemia), WBC (leukopenia), lymphocytes (lymphopenia), neutrophils (neutropenia), and platelets (thrombocytopenia).
- Chemistry: albumin (hypoalbuminemia), alkaline phosphatase (alkaline phosphatase increased), ALT, AST, total bilirubin (blood bilirubin increased), corrected calcium (hypocalcemia, hypercalcemia), creatinine (creatinine increased), magnesium (hypermagnesemia, hypomagnesemia), potassium (hyperkalemia, hypokalemia), and sodium (hyponatremia, hypernatremia).
- Coagulation: aPTT, INR.

Where corrected calcium is derived with the following formula:

Corrected calcium (mmol/L) = (0.02 * (40 (g/L) – normal albumin (g/L))) + serum calcium (mmol/L).

A summary of maximum severity observed on-study treatment for all parameters noted above will be generated for the coded hematology and chemistry parameters. Patients will only be included once, in the maximum severity, for each laboratory parameter. Additionally, a shift summary of baseline to maximum severity on-study treatment will also be produced. All patients in safety population will be included, patients without an assessment present at baseline or on-study treatment will be included as a missing category.

Laboratory measurements that are within their institutional limits of normal and are not graded as 1-4, per the CTCAE, will be summarized as "Grade 0," which is defined as normal. Additionally, if a lab parameter is graded in both directions (e.g. glucose: hyperglycemia and hypoglycemia), then low direction toxicity grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity, and vice versa.

Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges). Furthermore, only the numeric part in laboratory values that contain non-numeric qualifiers, such as less than (<) a certain value, or greater than (>) a certain value, will be used in the summary statistics.

Liver function tests: ALT, AST, and total bilirubin are used to assess possible drug induced liver toxicity.

Summary of liver function tests will include the following categories. The number and percentage of patients with each of the following during the treatment period will be summarized by treatment group:

- ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST ≥ 3×ULN, AST ≥ 5xULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- Total bilirubin ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and total bilirubin ≥ 2×ULN
- Concurrent AST ≥ 3×ULN and total bilirubin ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and total bilirubin ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and total bilirubin ≥ 2×ULN and ALP > 2×ULN
- Potential Hy's law: Concurrent (ALT or AST) ≥ 3×ULN and total bilirubin ≥ 2×ULN and ALP < 2×ULN or missing

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, i.e., a patient with an elevation of AST ≥ 10×ULN will also appear in the categories ≥ 5×ULN and ≥ 3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency and percentage.

By-patient listings will be presented for hematology, coagulation factors, thyroid function, pregnancy, urinalysis and serum chemistry.

13.5.4 Vital Signs

Diastolic and systolic blood pressure (mmHg), body temperature (°C), pulse rate (beats/min), and weight at each visit (up through Month 6), change from baseline to each post-baseline visit, post-baseline maximum/minimum, and change from baseline to post-baseline maximum/minimum will be summarized for the safety analysis set using descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum). Height, collected at baseline, will be summarized.

A by-patient listing of vital signs will be provided by patient ID number and visit in chronological order.

13.5.5 Physical Examinations and Other Observations Related to Safety

ECOG parameters will be presented at baseline, at each post-baseline time point, and at the end of treatment. The ECOG shift from baseline to highest score during the treatment period will be summarized.

Pregnancy test results and physical examinations will be presented in by-patient listings.

13.5.6 ECG

The following analyses will be performed for each applicable ECG parameters (RR, ECG PR, QRS, QT, ventricular rate -denoted as HR in what follows, QTcB and QTcF) by treatment group, during the treatment period.

- For each of the ECG parameters (HR, RR, QT, QTcF, QTcB, QRS, ECG PR intervals), descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point as well as maximum change from baseline. For QTcF and QTcB, the 90% CI of mean change from baseline will also be provided.
- Frequency (number and percentage) of patients with notable ECG values according to the following categories presented in Table 2.

Table 2: Notable ECG Values for QTc Interval Prolongation

TEST	Notable ECG Values
Heart Rate	≤ 50 bpm and decrease from baseline ≥ 20 bpm ≥ 120 bpm and increase from baseline ≥ 20 bpm
ECG PR Interval	≥ 220 ms and increase from baseline ≥ 20 ms
QRS	≥ 120 ms
QTcF and QTcB Absolute	430-449 msec 450- 479 msec 480- 499 msec ≥500 msec
QTc change from baseline	Increase from baseline > 30 ms and ≤ 60 ms Increase from baseline > 60 ms

Frequency (number and percentage) of patients with post-baseline qualitative ECG abnormalities (morphology) will be summarized.

Patients with notable ECG interval values and qualitative ECG abnormalities will be listed for each patient and time point and the corresponding notable values and abnormality findings will be included in the listings.

13.6 Efficacy Analyses

The analyses for efficacy endpoints using RECIST 1.1 and irRECIST will be based on the efficacy population, respectively as defined in section 9.3. The analysis for OS will be based on safety

population. Table 3 summarizes the key analysis for each part of the study. [redacted]

Table 3: Outputs produced for RECIST 1.1 and irRECIST

Endpoints	PART B		
	EC (Cohort A1 and A2)	[redacted]	[redacted]
RECIST 1.1			
ORR	X		X
DCR	X		X
DoR	X		X
PFS	X		X
irRECIST			
irORR	X		X
irDCR	X		X
irDoR	X		X
irPFS	X		X
OS	X		X

*CSR for Cohort E will be a safety-only synoptic CSR, there will be no efficacy analysis performed on this cohort.

13.6.1 ORR/irORR

All analyses will include summary statistics, including number of patients (n) and percentage (%) for categorical variables and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided exact 95% CIs will be provided for ORR and irORR.

Tumor burden (sum of longest diameters of target lesions) will be presented graphically using waterfall plots, to present each subject's best percentage change in tumor size as a separate bar, with the bars ordered from the largest increase to the largest decrease. For irRECIST the plot will present the sum of the target lesions and measurements of any new lesions that were considered as target lesions.

For a new lesion to be considered as a target lesion, the first appearance of given new lesion has to meet the following criteria

- lymph node must be ≥15mm in short axis
- non-lymph node must be ≥10mm in longest diameter

The exploratory analysis of ORR based on RECIST 1.1 will be performed for each of the following subgoups

- MSI status by FoundationOne NGS test (MSI-H vs. MSS vs. Unknown)
- # of prior therapy: (1 vs. ≥2)
- Prior Radiation: (Yes vs. No)
- Best overall response from last platinum-containing prior anti-cancer therapy (CR/PR vs. SD vs. PD vs. missing)
- Progression free interval from last platinum-containing prior anti-cancer therapy (<6 mon vs. >=6 mon vs. missing)

- Prior Bevacizumab use: (Yes vs. No)
- Tumor Type: Cohort F dMMR patients only
- dMMR subjects only in Cohort F only

13.6.2 **DoR/irDoR**

Analyses will be performed using KM methods and summarized by min, max, 25th, 50th (median), and 75th percentiles with associated 95% CI's as well as the number and percent of events, number and percent of censored observations. Censoring rules for DOR/irDOR are as noted in Table 4.

Swimmer plots for patients who achieve BOR of PR or better will be produced. This depicts each patient's nature (ongoing, all response), duration of exposure and duration of response will be presented separately.

The exploratory analysis of DoR based on RECIST 1.1 will be performed for each of the following subgoups

- MSI status by FoundationOne NGS test (MSI-H vs. MSS vs. Unknown)
- # of prior therapy: (1 vs. ≥2)
- Prior Radiation: (Yes vs. No)
- Best overall response from last platinum-containing prior anti-cancer therapy (CR/PR vs. SD vs. PD vs. missing)
- Progression free interval from last platinum-containing prior anti-cancer therapy (<6 mon vs. >=6 mon vs. missing)
- Prior Bevacizumab use: (Yes vs. No)
- [redacted]

Table 4: Censoring Rules for DOR/irDOR, PFS/irPFS.

Scenario	Date of event/censoring	Outcome
No baseline assessment	First dose date	Censored
No post-baseline evaluable radiologic tumor assessment	First dose date	Censored
Prior to 48 weeks tumor assessment: Progression or death ≤ 12 weeks +10 days after prior post-baseline tumor assessment or ≤ 18 weeks after first dose date After 48 weeks tumor assessment: Progression or death ≤24 weeks + 10 days after prior post-baseline tumor assessment	Date of progression or death	Event
Prior to 48 weeks tumor assessment: Progression or death > 12 weeks + 10 days after the prior post-baseline tumor assessment After 48 weeks tumor assessment: Progression or death >24 weeks + 10 days after the prior post-baseline tumor assessment	Date of last evaluable radiologic tumor assessment prior to Progression or death	Censored [a]
No progression	Date of last evaluable radiologic tumor assessment	Censored
New anticancer therapy given	Date of last evaluable radiologic tumor assessment before anticancer therapy given	Censored

[a] Tumor assessment is based on a CT or MRI scan. If progression/death is determined and 2 previous scans were missing, date of progression is not known.

13.6.3 DCR/irDCR

All analyses will include summary statistics, including number of patients (n) and percentage (%) for categorical variables and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided exact 95% CIs will be provided for DCR and irDCR.

13.6.4 PFS/irPFS

PFS/irPFS analyses will be performed using KM methods and summarized by 25th, 50th (median), and 75th percentiles with associated 95% CI's as well as the number and percent of events, number and percent of censored observations. Censoring rules for PFS/irPFS are as noted in Table 4.

13.6.5 OS

OS analyses will be performed using KM methods and summarized by 25th, 50th (median), and 75th percentiles with associated 95% CI's as well as the number and percent of events, number and percent of censored observations. Censoring for OS will be set at the last known date of contact.

13.7 Analyses of Patient Reported Outcomes

The PRO related analyses are detailed in a separate document: PRO analysis plan.

13.8 Exploratory Analyses

13.8.1 **Biomarker Analyses**

For each patient in Part 2B of the study, blood and tumor samples may be prospectively collected, evaluated and archived to support exploratory biomarker analysis. Tumor mutational burden (TMB) and PD-L1 status, if available, will be provided in the listing together with ORR/irORR.

13.9 Methods for Handling Dropouts and Missing Data

Missing observations will generally be treated as missing at random and will not be imputed, unless otherwise noted. Adverse event and concomitant medication dates will be imputed as mentioned in Section 11.3. If AE relationship is missing, it will be considered as related to medication in question. Note, for all listings the actual value for date (not imputed) will be presented in all data listings and imputed dates will only be used for programming flags.

13.10 Multiplicity

Adjustments for multiplicity will not be made since this is an estimation study. Separate inferences will be drawn for each tumor cohort.

13.11 Pooling of Sites

All data from all sites will be pooled.

14.0 **Validation**

PRA Health Sciences quality control procedures will be documented separately in the study-specific quality control plan.

- Derived datasets will be independently reprogrammed by a second programmer. The separate datasets produced by the 2 programmers must match 100%. Detailed specifications for the derived datasets are documented in the study Data Mapping Tool provided to the client at study conclusion.
- Tables will be independently quality controlled by a second programmer for numeric results.
- Figures will be checked for consistency against corresponding tables and listings, or independently reprogrammed if there are no corresponding tables or listings.
- Listings will be double programmed and checked for consistency against corresponding tables, figures, and derived datasets.

The entire set of TFL will be checked for completeness and consistency prior to its delivery to the client by the lead clinical programmer, the lead statistician, and a senior level or above statistician, who is not a member of the project team.

The PRA Health Sciences validation process will be repeated any time TFL are redelivered using different data. Execution of this validation process is documented through the study Table of Programs.

Appendix 1: List of Abbreviations

Abbreviation	Definition
ADA	antidrug antibody
ADI	actual dose intensity
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	below the level of quantification
BMI	body mass index
BOR	best overall response
C	Cycle
CBC	complete blood count
CI	confidence interval
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DL	dose level
DOR	duration of response
EC	Endometrial cancer
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End-of-treatment
FT3	free triiodothyronine
FT4	free thyroxine
HLT	high level term
HER2	human epidermal growth factor receptor
HRQoL	Health Related Quality of Life
ICF	informed consent form
INR	International normalized ratio
irAE	immune-related adverse events
irBOR	immune-related best overall response
irCR	immune-related complete response

Abbreviation	Definition
irDCR	immune-related disease control rate
irDOR	immune-related duration of response
irORR	immune-related objective response rate
irPFS	immune-related progression-free survival
irPD	immune-related progressive disease
irPR	immune-related partial response
irSD	immune-related stable disease
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
ISPD	Important and Significant Protocol Deviations
IV	intravenous(ly)
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MSI-H	microsatellite instability-high
MSS	microsatellite stable
MRI	magnetic resonance imaging
NC	not calculated
NCI	National Cancer Institute
ND	no disease
NE	Not evaluable
[redacted]	[redacted]
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death ligand-1
PDy	Pharmacodynamic
PFS	progression-free survival
PK	Pharmacokinetics
POLE-mut	Mutations in the exonuclease domain of polymerase ε
PR	partial response
PRO	Patient Reported Outcome
PT	preferred term
Q1	first quartile
Q2W	every 2 weeks
Q3	third quartile
Q3W	every 3 weeks
Q6W	every 6 weeks
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation	Definition
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical analysis plan
SD	stable disease
SOC	system organ class
SqCC	squamous-cell carcinoma
T3	Triiodothyronine
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listings
TIL	tumor-infiltrating lymphocytes
TMB	tumor mutational burden
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cell

Appendix 2: Common Terminology Criteria For Adverse Events V4.03 (CTCAE)

Lab Test Name	Lab Test Code	Standard Unit	CTCAE v4.03 SOC	CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	HGB	g/L	Blood and lymphatic system disorders	Anemia	<LLN - 100 g/L	<100 - 80g/L	<80 g/L	
Leukocytes	WBC	10^9/L	Investigations	White blood cell decreased	<LLN - 3.0 × 10^9/L	<3.0 - 2.0 × 10^9/L	<2.0 - 1.0 × 10^9 /L	<1.0 × 10^9/L
Platelets	PLAT	10^9/L	Investigations	Platelet count decreased	<LLN - 75.0 × 10^9/L	<75.0 - 50.0 × 10^9/L	<50.0 - 25.0 × 10^9/L	<25.0 × 10^9/L
Neutrophils	NEUT	10^9/L	Investigations	Neutrophil count decreased	<LLN - 1.5 × 10^9/L	<1.5 - 1.0 × 10^9/L	<1.0 - 0.5 × 10^9/L	<0.5 × 10^9/L
Lymphocytes	LYM	10^9/L	Investigations	Lymphocyte count decreased	<LLN - 0.8 x10^9 /L	<0.8 - 0.5 × 10^9 /L	<0.5 - 0.2 × 10^9 /L	<0.2 × 10^9 /L
Lymphocytes	LYM	10^9/L	Investigations	Lymphocyte count increased		>4x10^9/L – 20*10^9/L	>20*10^9/L	
Sodium	SODIUM	mmol/L	Metabolism and nutrition disorders	Hyponatremia	<LLN - 130 mmol/L		<130 - 120 mmol/L	<120 mmol/L
Sodium	SODIUM	mmol/L	Metabolism and nutrition disorders	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Potassium	K	mmol/L	Metabolism and nutrition disorders	Hypokalemia	<LLN - 3.0 mmol/L		<3.0 - 2.5 mmol/L	<2.5 mmol/L
Potassium	K	mmol/L	Metabolism and nutrition disorders	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Creatinine	CREAT	umol/L	Investigations	Creatinine increased	>ULN - 1.5 × ULN	>1.5 - 3.0 × ULN	>3.0 - 6.0 × ULN	>6.0 × ULN
Glucose	GLUC	mmol/L	Metabolism and nutrition disorders	Hypoglycemia	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L
Glucose	GLUC	mmol/L	Metabolism and nutrition disorders	Hyperglycemia	>ULN - 8.9 mmol/L	>8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L	>27.8 mmol/L
Bilirubin	BILI	umol/L	Investigations	Blood bilirubin increased	>ULN - 1.5 × ULN	>1.5 - 3.0 × ULN	>3.0 - 10.0 × ULN	>10.0 × ULN
Alanine Aminotransferase	ALT	U/L	Investigations	Alanine aminotransferase increased	>ULN - 3.0 × ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 × ULN
Aspartate Aminotransferase	AST	U/L	Investigations	Aspartate aminotransferase increased	>ULN - 3.0 × ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 × ULN
Calcium (corrected)	CA	mmol/L	Metabolism and nutrition disorders	Hypocalcemia	<LLN - 2.0 mmol/L	<2.0 - 1.75 mmol/L	<1.75 - 1.5 mmol/L	<1.5 mmol/L
Calcium (corrected)	CA	mmol/L	Metabolism and nutrition disorders	Hypercalcemia	>ULN - 2.9 mmol/L	>2.9 - 3.1 mmol/L	>3.1 - 3.4 mmol/L	>3.4 mmol/L
Albumin	ALB	g/L	Metabolism and nutrition disorders	Hypoalbuminemia	<LLN - 30 g/L	<30 - 20 g/L	<20 g/L	
Prothrombin Intl. Normalized Ratio	INR		Investigations	INR increased	>1 - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	
QTc	QTc	Ms	Electrocardiogram QT corrected interval prolonged		450 - 480 ms	481 - 500 ms	>=501ms	

Lab Test Name	Lab Test Code	Standard Unit	CTCAE v4.03 SOC	CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
Magnesium	MG	mmol/L	Metabolism and nutrition disorders	Hypomagnesemia	<LLN - 0.5 mmol/L	<0.5 - 0.4 mmol/L	<0.4 - 0.3 mmol/L	<0.3 mmol/L;
Magnesium	MG	mmol/L	Metabolism and nutrition disorders	Hypermagnesemia	>ULN - 1.23 mmol/L	-	>1.23 - 3.30 mmol/L	>3.30 mmol/L;
Alkaline phosphatase	ALP	U/L	Investigations	Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Activated partial thromboplastin time	APTT	S	Investigations	Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN;	-

Appendix 3: Laboratory Standard Units

Laboratory Test	**SI Unit**
Albumin	g/L
Alkaline Phosphatase	U/L
Absolute neutrophil count	10^9/L
Basophils	10^9/L
Bicarbonate	mmol/L
Total Bilirubin	µmol/L
Blood Urea Nitrogen	mmol/L
Calcium	mmol/L
Chloride	mmol/L
Creatinine	µmol/L
Eosinophils	10^9/L
Glucose	mmol/L
Granulocytes	10^9/L
Hematocrit	frac of 1
Hemoglobin	g/L
INR	frac of 1
Lymphocytes	10^9/L
Magnesium	mmol/L
Mean Corpuscular Hemoglobin	pg
Mean Corpuscular Volume	fL
Monocytes	10^9/L
Platelets	10^9/L
Potassium	mmol/L
Total Protein	g/L
Prothrombin Time	s
Partial Thromboplastin Time	s
Red Blood Cells	10^{12}/L
Aspartate Transaminase	U/L
Alanine Transaminase	U/L
Sodium	mmol/L
White Blood Cells	10^9/L

Appendix 4: Response Evaluation Criteria In Solid Tumors (RECIST), V1.1

Response Criteria by RECIST v1.1

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

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

Table 5: RECIST 1.1 Response for Patients with Measurable Disease (i.e, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	> 4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	> 4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once > 8 wks. from baseline**
PD	Any	Yes	PD	No prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

* See RECIST v1.1 publication (Eisenhauer et al., 2009) for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint. In study 4010-01-001 tumor assessment is scheduled for 12 weeks ±10 days as per the Study Protocol.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

Table 6: RECIST 1.1 Response For Patients with Non-Measurable Disease only (i.e, Non- Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; PD = progressive disease

*'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Appendix 5: Immune-Related Response Evaluation Criteria In Solid Tumors

Immune-related RECIST will be used by local site Investigators to assess tumor response and progression and make treatment decisions.

Table 7 provides guidelines for determining objective response incorporating irRECIST. Further details provided in the protocol in Section 6.3.1.4.

Table 7 Imaging and Treatment after First Radiologic Evidence		**Confirmation of Response**
irCR	Disappearance of all measurable and non-measurable lesions. Lymph nodes must have reduction in short axis to < 10 mm.	Required
irPR	At least 30% decrease in the sum of diameters of measurable lesions, taking as reference the baseline sum diameters.	Required
irSD	Shrinkage does not qualify for irCR/irPR or increase does not qualify for irPD.	Not required
irPD	At least 20% increase and absolute increase of at least 5 mm increase in sum of the diameters of measurable lesions. The appearance of new lesions is not considered PD, but are to be included in the sum diameters.	Confirmation required at least 4 weeks after the first irPD assessment provided the patient is considered clinically stable (see protocol Section 6.3.1.5).

Abbreviations: irCR = immune-related complete response; irPR = immune-related partial response; irSD = immune- related stable disease; irPD = immune-related progressive disease; PD = progressive disease

Source: Nishino et al., 2015. [4]

Appendix 6: Immune-Related Adverse Events

Below is a list of MedDRA preferred terms that will be used to identify immune-related adverse events.

Immune-mediated Pulmonary
Pneumonitis
Sarcoidosis
Immune-mediated Gastro intestinal
Colitis
Diarrhoea
Gastroenteritis
Enteritis
Gastritis
Duodenitis
Immune-mediated hepatic
Autoimmune hepatitis
Hepatitis
Hepatitis toxic
Liver injury
Transaminases increased
Aspartate aminotransferase increased
Alanine aminotransferase increased
Blood bilirubin increased
Hyperbilirubinaemia
Hepatic enzymes increased
Immune-mediated endocrinopathies
Hyperthyroidism
Hypothyroidism
Thyroid disorder

Thyroiditis
Hypophysitis
Hypopituitarism
Adrenal insufficiency
Secondary adrenocortical insufficiency
Type I diabetes mellitus
Diabetic ketoacidosis
Hyperglycaemia
Immune-mediated renal
Nephritis
Renal impairment
Blood creatinine increased
Immune-mediated skin adverse reactions
Rash
Rash maculo-papular
Rash macular
Rash erythematous
Rash papular
Rash pruritic
Rash pustular
Erythema
Exfoliative rash
Dermatitis exfoliative
Autoimmune dermatitis
Pemphigoid
Vitiligo
Pruritus
Steven-Johnson syndrome
Toxic epidermal necrolysis

Immune-mediated pancreatitis
Pancreatitis
Pancreatitis acute
Autoimmune pancreatitis
Amylase increased
Lipase increased
Immune-mediated hematologic
Aplastic anaemia
Autoimmune haemolytic Anaemia
Haemolytic anaemia
Immune-mediated musculo skeletal
Arthralgia
Arthritis
Myositis
Polymyalgia rheumatica
Rhabdomyolysis
Immune-mediated nervous system
Autoimmune neuropathy
Polyneuropathy
Neuropathy peripheral
Peripheral sensory neuropathy
Hypoaesthesia
Paraesthesia
Facial paresis
Dysaesthesia
Demyelination
Myelitis
Encephalitis autoimmune
Seizure

Guillain-Barre syndrome
Motor dysfunction
Myasthenia gravis
Myasthenic syndrome
Immune mediated Ocular
Iridocyclitis
Uveitis
Iritis
Immune mediated cardio vascular
Myocarditis
Vasculitis
Pericarditis
Hypersensitivity
Hypersensitivity
Infusion related reaction
Anaphylactic reaction
Drug hypersensitivity
Type I hypersensitivity
Immune mediated others
Histiocytosis haematophagic
Histiocytosis
Histiocytic necrotising lymphadenitis
Systemic inflammatory response syndrome
Vogt-Koyanagi-Harada syndrome

Appendix 7: Schedule of Events

Part 2B Schedule of Events

	Q3W Dose Schedule					Q6W Dose Schedule									
Cycle/Visit:	Screening	Cycle 1[a]	Cycle 2[a]	Cycle 3[a]	Cycle 4[a]	Cycle 5[a]	Cycle 6[a]	Cycle 7[a]	Cycle 8[a]	Cycle 9[a]	Cycle 10[a]	Cycle n[a]	EOT[b]	Safety FUP[c]	FUP Assessments (every 90±14 days)
Day: Day: Procedure:	-35 to -1	1	1	1	1	1	1	1	1	1	1	1	30 or 42±7 days	90±7 days	
Informed consent[d]	X														
Inclusion/exclusion criteria review	X	X													
Demographics	X														
Medical, surgical, cancer, and medication history	X														
Blood sample for PK/ADA[e]		X[e]			X[e]	X[e]			X[e]			X[e]		X[e]	
Blood sample for exploratory biomarkers[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]						X[e]		
Blood sample for exploratory ctDNA[e]		X[e]													
Blood sample for MSI testing (Cohort A1, A2, and F only)[e]		X[e]													

Part 2B Schedule of Events (Continued)

	Q3W Dose Schedule					Q6W Dose Schedule									
Cycle/Visit:	Screening	Cycle 1[a]	Cycle 2[a]	Cycle 3[a]	Cycle 4[a]	Cycle 5[a]	Cycle 6[a]	Cycle 7[a]	Cycle 8[a]	Cycle 9[a]	Cycle 10[a]	Cycle n[a]	EOT[b]	Safety FUP[c]	FUP Assessments (every 90±14 days)
Day: Day: Procedure:	-35 to -1	1	1	1	1	1	1	1	1	1	1	1	30 or 42±7 days	90±7 days	
Required Tumor Biopsy[f]	X														
Optional Tumor Biopsy[g]	X			X									X		
Tumor assessment (irRECIST)[h]	X[h]					X	X	X	X	X	X	X[h]	X	X	
PRO assessments (Cohorts A1 and F)[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[v]
Laboratory assessments:															
CBC w/differential	X[j]	X[k,l]	X[l,m]	X[l,m]	X[l,m]	X[l,m]	X[l,m]	X[l,m]	X[l,m]	X[l,m]	X[l,m]	X[l,m]	X	X	
Serum chemistry	X[j]	X[k,l]	X[l,m]	X[l,m]	X[l,m]	X[l,m]	X[l,m]	X[l,m]	X[l,m]	X[l,m]	X[l,m]	X[l,m]	X	X	
Coagulation	X[j]	X[n]													
Pregnancy test[o]	X[j]	X[k,l]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	
HBV/HCV test[p]	X														
Serum-based tumor markers (eg, CA125)[h]	X[j,k]					X	X	X	X	X	X	X[h]	X		
Urinalysis	X[j,k]			X[l,m]		X[l,m]	X[l,m]	X[l,m]	X[l,m]	X[l,m]	X[l,m]	X[l,m]	X	X	
Thyroid panel[q]	X[j]		X		X		X	X	X	X	X	X	X		

Part 2B Schedule of Events (Continued)

	Q3W Dose Schedule					Q6W Dose Schedule									
Cycle/Visit:	Screening	Cycle 1[a]	Cycle 2[a]	Cycle 3[a]	Cycle 4[a]	Cycle 5[a]	Cycle 6[a]	Cycle 7[a]	Cycle 8[a]	Cycle 9[a]	Cycle 10[a]	Cycle n[a]	EOT[b]	Safety FUP[c]	FUP Assessments (every 90±14 days)
Day: Day: Procedure:	-35 to -1	1	1	1	1	1	1	1	1	1	1	1	30 or 42±7 days	90±7 days	
ECG[f]	X[j r]	X[r]			X[r]	X[r]			X[r]			X[r]	X[r]		
Physical examination	X[j]												X	X	
Symptom-directed PE[l]		X	X	X	X	X	X	X	X	X	X	X			
Vital signs, height, and weight[s]	X[j]	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG performance status	X		X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications	X														
AE monitoring	X[l t]														
TSR-042 administered[m]		X	X	X	X	X	X	X	X	X	X	X			
Survival follow up and post-study new cancer therapy assessment														X	X[v]

Abbreviations: ADA=antidrug antibody; AE=adverse event; CBC=complete blood count; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End-of-treatment; FUP=follow-up; HBV=hepatitis B virus; HCV=hepatitis C virus; ICF=informed consent form; irRECIST=immune-related RECIST; IV=intravenous; MRI=magnetic resonance imaging; MSI=microsatellite instability; OC=ovarian cancer; PDy=pharmacodynamics; PE=physical examination; PK=pharmacokinetics; Q3W=every 3 weeks; Q6W=every 6 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event.

Note: All procedures are to take place within a ±7 day window unless otherwise indicated.

[a] Treatment cycles are 21 ± 7 days in duration for Cycle 1 through Cycle 4. Treatment cycles are 42 ± 7 days in duration for Cycle 5 and all subsequent cycles. One dose of TSR-042 will be administered on Day 1 of every cycle. One dose=one cycle.

[b] EOT visit should be completed 30 days (Q3W schedule) or 42 days (Q6W schedule) (±7) days after last study drug dose. Patients with ongoing AEs will be followed until resolution or stabilization of the AE.

[c] Safety follow-up visit should be conducted 90 (±7) days after last study drug dose unless new anticancer therapy, has been initiated. Patients with ongoing AEs will be followed until resolution or stabilization of the AE.

[d] The ICF may be signed prior to the 35-day screening period.

[e] Refer to Protocol Table 10 for the detailed sample collection schedule.

[f] Patients are required to have tumor tissue available (archival or newly obtained biopsy) prior to start of study treatment.

[g] For patients who consent to optional serial biopsies, the biopsies will be obtained prior to initiation of study treatment, approximately 4-6 weeks following the first TSR-042 dose, EOT visit, and whenever possible, at the time of disease progression (note: while the biopsy is voluntary, it is highly encouraged). A core biopsy is recommended (details are provided in the Study Manual); if an excisional or incisional biopsy is to be performed, it must be conducted on a non-target lesion. If a patient has had a biopsy prior to screening and within 12 weeks of study treatment, that biopsy may be accepted as the screening biopsy.

[h] Tumor assessment per irRECIST via CT or MRI (chest, abdomen, and pelvis) is required at screening within 28 days of the first dose, 12 weeks after the first TSR-042 dose (84 ±10 days), and every 6 weeks (42 ±10 days) thereafter while on study treatment independent of cycle delays and/or dose interruptions, and/or at any time when progression of disease is suspected (a final set of radiographic images is required at the time of disease progression, if not done within the last 4 weeks). Appropriate testing of serum tumor markers (e.g., CA-125 for OC patients) should also be conducted 12 weeks after the first TSR-042 dose (84 ±10 days), and every 6 weeks (42 ±10 days) thereafter, and as clinically indicated. Brain scan will be conducted if clinically indicated. Bone scans will be conducted per standard of care. After 1 year, patients who remain on treatment will have imaging performed every 12 weeks (84 ±10 days). If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, imaging scans and appropriate serum-based tumor marker testing (e.g., CA-125 for OC patients) should continue at the specified intervals. All radiographic images/scans will be sent to a central imaging vendor upon acquisition and archived for potential future evaluation. Per irRECIST, complete response (CR) or partial response (PR) should be confirmed; tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated. In addition, it is highly recommended that PD should be confirmed a minimum of 4 weeks and up to 6 weeks after the first PD assessment. Clinically stable patients should not be discontinued until progression is confirmed (see Protocol Section 6.3.1.5 and Protocol Appendix B).

[i] PROs should be collected before conducting any other procedures and will be performed only for patients in Cohorts A1 and F enrolled under Amendment 3 or subsequent amendments.

[j] Standard of care tests/procedures, scans, laboratory assessments, ECGs, physical examinations, vital signs, height, and weight performed prior to the patient signing the ICF can be used as part of the screening assessments as long as the tests/procedures meet the protocol-required timelines (i.e., within 35 days of first dose for these procedures with the exception of the pregnancy test, which must be conducted within 72 hours of first dose date, and the baseline tumor assessments scans, which must be done within 28 days of the first dose) and any relevant guidelines (e.g., diagnostic quality for scans).

[k] If screening laboratory testing (CBC, serum chemistry, serum-based tumor markers, urinalysis) performed within 72 hours prior to the date of first dose of study treatment on Day 1, repeat testing is not required.

[l] Sample collection/procedure must be performed prior to TSR-042 administration during treatment visit.

[m] Samples can be collected up to 72 hours prior to TSR-042 administration.

[n] To be conducted per standard of care for patients on anticoagulant therapy.

[o] Negative serum pregnancy test required within 72 hours prior to date of the first dose of study treatment on Day 1 for females of childbearing potential; urine pregnancy test must be conducted within 72 hours prior to the first dose of study treatment on Day 1 of every cycle for the duration of the study, at the 30-day (Q3W schedule) or 42-day (Q6W schedule) EOT visit, and at the 90-day Safety FUP visit. Pregnancy status obtained at 90-day safety follow-up visit can be used for FUP assessment. Pregnancy status will be reported through Day 150 post-treatment.

[p] Only when medically indicated based on history and physical examination.
[q] Blood samples for the thyroid panel (i.e., TSH, T3 or FT3, FT4, or equivalent tests) are to be collected during screening, Cycle 2/Day 1, Cycle 4/Day 1, Cycle 6/Day 1, and every 6 weeks thereafter through the remainder of the study (blood samples can be collected up to 7 days prior to TSR-042 administration).
[r] Patients will undergo ECG monitoring by 12-lead ECG evaluations with triplicate readouts at screening, pre-dose and at 0.5h (end of infusion) on Day 1 of Cycles 1, 4, 5, 8, and 12, at the EOT visit, and if clinically indicated.
[s] Vital signs include blood pressure, pulse, and temperature. Height obtained at screening only.
[t] AEs and SAEs are required to be captured through 90 days after cessation of study treatment (or until the start of alternate anticancer therapy, whichever occurs first), and any pregnancies that occur within 150 days post-treatment are to be reported.
[u] Administer TSR-042 on Day 1 of each cycle.
[v] Follow up assessments should be conducted over telephone every 90 (± 14) days after the last study drug dose. Survival status obtained at 90-day safety follow-up visit can be used for FUP assessment.

Appendix 8: Table of Contents for Tables, Figures and Listings by Cohort

TFL Flag	Master Table Shell ID	Master Shell Title	Cohort A1 and A2 (Y/N)	[redacted]	[redacted]
T	Table 1.1	<Table 1.1> Patient Populations (Screening Analysis Set)	Y	N	Y
T	Table 1.2	<Table 1.2> Enrollment by Center (Safety Analysis Set)	Y	N	Y
T	Table 1.3	<Table 1.3> Patient Disposition (Safety Analysis Set)	Y	Y	Y
T	Table 1.4	<Table 1.4> Important and Significant Protocol Deviations (Safety Analysis Set)	Y	Y	Y
T	Table 1.5.1	<Table 1.5.1> Demographic Characteristics (Safety Analysis Set)	Y	Y	Y
T	Table 1.5.2	<Table 1.5.2> Demographic Characteristics (Primary Efficacy Analysis Set)	Y	N	Y
T	Table 1.6.1	<Table 1.6.1> Primary Cancer History – Endometrial (Safety Analysis Set)	Y	N	N
T	Table 1.6.2	<Table 1.6.2> Primary Cancer History – Endometrial (Primary Efficacy Analysis Set)	Y	N	N
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T	Table 1.9	<Table 1.9> General Medical History by System Organ Class and Preferred Term (Safety Analysis Set)	Y	Y	Y
T	Table 1.10	<Table 1.10> Prior Non-Anti-Cancer Medications by ATC Classification and WHO Drug Dictionary Preferred Name (Safety Analysis Set)	Y	Y	Y
T	Table 1.11	<Table 1.11> Concomitant Medications by ATC Classification and WHO Drug Dictionary Preferred Term (Safety Analysis Set)	Y	Y	Y
T	Table 1.12.1	<Table 1.12.1> Prior Anticancer Treatment for Primary Cancer (Safety Analysis Set)	Y	Y	Y
T	Table 1.12.2	<Table 1.12.2> Prior Anticancer Treatment for Primary Cancer (Primary Efficacy Analysis Set)	Y	N	Y
T	Table 1.13.1	<Table 1.13.1> Prior Anticancer Treatment Summary for Primary Cancer (Safety Analysis Set)	Y	Y	Y

TFL Flag	Master Table Shell ID	Master Shell Title	Cohort A1 and A2 (Y/N)	[redacted]	[redacted]
T	Table 1.13.2	<Table 1.13.2> Prior Anticancer Treatment Summary for Primary Cancer (Primary Efficacy Analysis Set)	Y	N	Y
T	Table 1.14	<Table 1.14> Patients on Treatment by Week Intervals (Safety Analysis Set)	Y	Y	Y
T	Table 1.15	<Table 1.15> Treatment Compliance and Exposure to dostarlimab (Safety Analysis Set)	Y	Y	Y
T	Table 2.1	<Table 2.1> Tumor response summary - RECIST v1.1 assessed by BICR (Primary Efficacy Analysis Set)	Y	N	Y
T	Table 2.2	<Table 2.2> Tumor response summary - irRECIST based on Investigator assessment (Secondary Efficacy Analysis Set)	Y	N	Y
T	Table 2.3	<Table 2.3> Tumor response summary by MSI Status - RECIST v1.1 assessed by BICR (Primary Efficacy Analysis Set)	Y	N	Y
T	Table 2.4	<Table 2.4> Tumor response summary by number of prior therapies - RECIST v1.1 assessed by BICR (Primary Efficacy Analysis Set)	Y	N	Y
T	Table 2.5	<Table 2.5> Tumor response summary by Prior Radiation Status - RECIST v1.1 assessed by BICR (Primary Efficacy Analysis Set)	Y	N	Y
T	Table 2.6	<Table 2.6> Tumor response summary by Best overall response from last platinum-containing prior anti-cancer therapy - RECIST v1.1 assessed by BICR (Primary Efficacy Analysis Set)	Y	N	Y
T	Table 2.7	<Table 2.7> Tumor response summary by Progression free interval from last platinum-containing prior anti-cancer therapy- RECIST v1.1 assessed by BICR (Primary Efficacy Analysis Set)	Y	N	Y
T	Table 2.8	<Table 2.8> Tumor response summary by Prior Bevacizumab Use - RECIST v1.1 assessed by BICR (Primary Efficacy Analysis Set)	Y	N	Y
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T	Table 2.10	<Table 2.10> Kaplan Meier Analysis of Progression Free Survival - RECIST v1.1 based on BICR (Primary Efficacy Analysis Set)	Y	N	Y
T	Table 2.11	<Table 2.11> Kaplan Meier Analysis of Progression Free Survival - irRECIST based on Investigator assessment (Secondary Efficacy Analysis Set)	Y	N	Y
T	Table 2.12	<Table 2.12> Kaplan Meier Analysis of Duration of Response - RECIST v1.1 based on BICR (Primary Efficacy Analysis Set - Patients with Objective Response)	Y	N	Y

TFL Flag	Master Table Shell ID	Master Shell Title	Cohort A1 and A2 (Y/N)	[redacted]	[redacted]
T	Table 2.13	<Table 2.13> Kaplan Meier Analysis of Duration of Response - irRECIST based on Investigators assessment (Secondary Efficacy Analysis Set - Patients with Objective Response)	Y	N	Y
T	Table 2.14	<Table 2.14> Kaplan Meier Analysis of Duration of Response by MSI status - RECIST v1.1 based on BICR (Primary Efficacy Analysis Set - Patients with Objective Response)	Y	N	Y
T	Table 2.15	<Table 2.15> Kaplan Meier Analysis of Duration of Response by number of prior therapies - RECIST v1.1 based on BICR (Primary Efficacy Analysis Set - Patients with Objective Response)	Y	N	Y
T	Table 2.16	<Table 2.16> Kaplan Meier Analysis of Duration of Response by Prior Radiation Status - RECIST v1.1 based on BICR (Primary Efficacy Analysis Set - Patients with Objective Response)	Y	N	Y
T	Table 2.17	<Table 2.17> Kaplan Meier Analysis of Duration of Response by Best overall response from last platinum-containing prior anti-cancer therapy - RECIST v1.1 based on BICR (Primary Efficacy Analysis Set - Patients with Objective Response)	Y	N	Y
T	Table 2.18	<Table 2.18> Kaplan Meier Analysis of Duration of Response by Progression free interval from last platinum-containing prior anti-cancer therapy- RECIST v1.1 based on BICR (Primary Efficacy Analysis Set - Patients with Objective Response)	Y	N	Y
T	Table 2.19	<Table 2.19> Kaplan Meier Analysis of Duration of Response by Prior Bevacizumab Use - RECIST v1.1 based on BICR (Primary Efficacy Analysis Set - Patients with Objective Response)	Y	N	Y
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T	Table 2.22	<Table 2.22> Kaplan Meier Analysis of Overall Survival (Safety Analysis Set)	Y	N	Y
T	Table 3.1.1	<Table 3.1.1> Overall summary of Treatment-emergent Adverse Events (Safety Analysis Set)	Y	Y	Y
T	Table 3.1.2	<Table 3.1.2> Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)	Y	Y	Y

TFL Flag	Master Table Shell ID	Master Shell Title	Cohort A1 and A2 (Y/N)	[redacted]	[redacted]
T	Table 3.1.3	<Table 3.1.3> Treatment-Emergent Adverse Events Experienced by ≥5% of Patients by System Organ Class and Preferred Term (Safety Analysis Set)	Y	Y	Y
T	Table 3.1.4	<Table 3.1.4> Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum CTCAE Grade (Safety Analysis Set)	Y	N	Y
T	Table 3.1.5	<Table 3.1.5> CTCAE Grade 3 or Greater Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)	Y	Y	Y
T	Table 3.1.6	<Table 3.1.6> Treatment-Related Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)	Y	Y	Y
T	Table 3.1.7	<Table 3.1.7> Treatment-Related Treatment-Emergent Adverse Events Experienced by ≥ 5% of Patients by Preferred Term (Safety Analysis Set)	Y	Y	Y
T	Table 3.1.8	<Table 3.1.8> Treatment-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum CTCAE Grade (Safety Analysis Set)	Y	N	Y
T	Table 3.1.9	<Table 3.1.9> CTCAE Grade 3 or Greater Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)	Y	Y	Y
T	Table 3.1.10	<Table 3.1.10> Patients with Adverse Events with Outcome of Death (Safety Analysis Set)	Y	Y	Y
T	Table 3.1.11	<Table 3.1.11> Serious Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)	Y	Y	Y
T	Table 3.1.12	<Table 3.1.12> Patients Who Experienced Serious Adverse Events (Safety Analysis Set)	Y	Y	Y
T	Table 3.1.13	<Table 3.1.13> Treatment-Related Serious Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)	Y	Y	Y
T	Table 3.1.14	<Table 3.1.14> Treatment-Emergent Adverse Events Leading to Withdrawal of Study Treatment by System Organ Class and Preferred Term (Safety Analysis Set)	Y	Y	Y
T	Table 3.1.15	<Table 3.1.15> Patients Who Experienced Treatment-Emergent Adverse Events Leading to Withdrawal of Study Treatment (Safety Analysis Set)	Y	Y	Y
T	Table 3.1.16	<Table 3.1.16> Treatment-Related Adverse Events Leading to Withdrawal of Study Treatment by System Organ Class and Preferred Term (Safety Analysis Set)	Y	Y	Y
T	Table 3.1.17	<Table 3.1.17> Treatment-Emergent Adverse Events leading to Study Treatment Infusion Interruption by System Organ Class and Preferred Term (Safety Analysis Set)	Y	Y	Y
T	Table 3.1.18	<Table 3.1.18> Treatment-Emergent Adverse Events leading to Study Treatment Interruption by System Organ Class and Preferred Term (Safety Analysis Set)	Y	Y	Y
T	Table 3.1.19	<Table 3.1.19> Treatment-Emergent Immune-Related Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)	Y	Y	Y

TFL Flag	Master Table Shell ID	Master Shell Title	Cohort A1 and A2 (Y/N)	[redacted]	[redacted]
T	Table 3.1.20	<Table 3.1.20> Treatment-Related Treatment-Emergent Immune-Related Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)	Y	Y	Y
T	Table 3.1.21	<Table 3.1.21> Summary of Deaths Observed During the Study (Safety Analysis Set)	Y	Y	Y
T	Table 3.1.22	<Table 3.1.22> Subgroup Analysis of Treatment-Emergent Adverse Events by number of Prior Therapies by System Organ Class and Preferred Term (Safety Analysis Set)	Y	N	Y
T	Table 3.1.23	<Table 3.1.23> Subgroup Analysis of Treatment-Emergent Adverse Events by Prior Radiation by System Organ Class and Preferred Term (Safety Analysis Set)	Y	N	Y
T	Table 3.1.24	<Table 3.1.24> Subgroup Analysis of Treatment-Emergent Adverse Events by Prior Bevacizumab by System Organ Class and Preferred Term (Safety Analysis Set)	Y	N	Y
T	Table 4.1	<Table 4.1> Hematology Results by Visit (Safety Analysis Set)	Y	N	Y
T	Table 4.2	<Table 4.2> Maximum Post Baseline Hematology Grade (Safety Analysis Set)	Y	N	Y
T	Table 4.3	<Table 4.3> Shift Summary of Hematology Results by Maximum CTCAE Grade (Safety Analysis Set)	Y	N	Y
T	Table 4.4	<Table 4.4> Chemistry Results by Time Point (Safety Analysis Set)	Y	N	Y
T	Table 4.5	<Table 4.5> Maximum Post Baseline Chemistry Grade (Safety Analysis Set)	Y	N	Y
T	Table 4.6	<Table 4.6> Shift Summary of Chemistry Results by Maximum CTCAE Grade (Safety Analysis Set-Part 2B)	Y	N	Y
T	Table 4.7	<Table 4.7> Urinalysis Results by Visit-Continuous Variables (Safety Analysis Set)	Y	N	Y
T	Table 4.8	<Table 4.8> Incidence of Potential Liver Toxicity Events (Safety Analysis Set)	Y	Y	Y
T	Table 5.1	<Table 5.1> Vital Sign Results by Visit (Safety Analysis Set)	Y	N	Y
T	Table 5.2	<Table 5.2> Electrocardiogram Results by Visit (Safety Analysis Set)	Y	N	Y
T	Table 5.3	<Table 5.3> Postbaseline Abnormal ECG Results (Safety Analysis Set)	Y	N	Y
T	Table 5.4	<Table 5.4> Patients with Abnormal Electrocardiogram Results (Safety Analysis Set)	Y	N	Y
T	Table 5.5	<Table 5.5> Shift Summary of the ECOG Performance Status from Baseline to Highest On-Treatment Score (Safety Analysis Set)	Y	N	Y
F	Figure 1.1	<Figure 1.1> Kaplan-Meier Plot for Progression Free Survival per RECIST 1.1 – Based on BICR Assessment (Primary Efficacy Analysis Set)	Y	N	Y

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F	Figure 1.2	<Figure 1.2> Kaplan-Meier Plot for Progression Free Survival per irRECIST – Based on Investigator's Assessment (Secondary Efficacy Analysis Set)	Y	N	Y
F	Figure 1.3	<Figure 1.3> Kaplan-Meier Plot for Duration of Response per RECIST 1.1 – Based on BICR Assessment (Primary Efficacy Analysis Set - Patients with Objective Response)	Y	N	Y
F	Figure 1.4	<Figure 1.4> Kaplan-Meier Plot for Duration of Response per irRECIST – Based on Investigator's Assessment (Secondary Efficacy Analysis Set- Patients with Objective Response)	Y	N	Y
F	Figure 1.5	<Figure 1.5> Kaplan-Meier Survival Plot for OS (Safety Analysis Set)	Y	N	Y
F	Figure 1.6	<Figure 1.6> Waterfall Plot of the maximum percentage change in target lesions, as compared with baseline measurements based on BICRper RECIST 1.1(Primary Efficacy Analysis Set)	Y	N	Y
F	Figure 1.7	<Figure 1.7> Waterfall Plot of the maximum percentage change in target lesions, as compared with baseline measurements based on investigator assessment per irRECIST (Secondary Efficacy Analysis Set)	Y	N	Y
F	Figure 1.8	<Figure 1.8> Duration of Treatment of Responders, Based on BICR according to RECIST 1.1 (Primary Efficacy Analysis Set)	Y	N	Y
F	Figure 1.9	<Figure 1.9> Duration of Treatment of Responders, Based on Investigator Assessment According to irRECIST (Secondary Efficacy Analysis Set)	Y	N	Y
F	Figure 1.10	<Figure 1.10> Duration of Response, based on BICR according to RECIST 1.1 (Primary Efficacy Analysis Set)	Y	N	Y
F	Figure 1.11	<Figure 1.11> Duration of Response, based on Investigator Assessment according to irRECIST (Secondary Efficacy Analysis Set)	Y	N	Y
L	Listing 1.1	<Listing 1.1> Analysis Set (Screening Analysis Set)	Y	N	Y
L	Listing 1.2	<Listing 1.2> Discontinued Patients (Safety Analysis Set)	Y	Y	Y
L	Listing 1.3	<Listing 1.3> Protocol Deviations (Safety Analysis Set)	Y	Y	Y
L	Listing 1.4	<Listing 1.4> Demographic and Baseline Data (Safety Analysis Set)	Y	Y	Y
L	Listing 1.5	<Listing 1.5> General Medical History (Safety Analysis Set)	Y	Y	Y
L	Listing 1.6	<Listing 1.6> Prior and Concomitant Medications (Safety Analysis Set)	Y	Y	Y
L	Listing 1.7	<Listing 1.7> Prior Surgery for Study Indication (Safety Analysis Set)	Y	Y	Y
L	Listing 1.8	<Listing 1.8> Previous Radiotherapy (Safety Analysis Set)	Y	Y	Y

TFL Flag	Master Table Shell ID	Master Shell Title	Cohort A1 and A2 (Y/N)	[redacted]	[redacted]
L	Listing 1.9	<Listing 1.9> Endometrial Cancer History (Safety Analysis Set)	Y	N	N
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
L	Listing 1.12	<Listing 1.12> Prior Anticancer Treatment for Primary Cancer (Safety Analysis Set)	Y	Y	Y
L	Listing 1.13	<Listing 1.13> Dostarlimab Compliance and Drug Dosing Data (Safety Analysis Set)	Y	Y	Y
L	Listing 1.14	<Listing 1.14> Dostarlimab Dose Intensity Data (Safety Analysis Set)	Y	Y	Y
L	Listing 1.15	<Listing 1.15> Individual Efficacy Results-RECIST v1.1 (Primary Efficacy Analysis Set)	Y	N	Y
L	Listing 1.16	<Listing 1.16> Individual Efficacy Results-irRECIST (Secondary Efficacy Analysis Set)	Y	N	Y
L	Listing 1.17	<Listing 1.17> Individual Tumor Target Lesion Assessment (Primary Efficacy Analysis Set)	Y	N	Y
L	Listing 1.18	<Listing 1.18> Individual Tumor Non-target lesion Assessment (Primary Efficacy Analysis Set)	Y	N	Y
L	Listing 1.19	<Listing 1.19> Individual New lesions assessment (Primary Efficacy Analysis Set)	Y	N	Y
L	Listing 1.20	<Listing 1.20> Overall response by visit (Subjects in either Primary of Secondary Efficacy Analysis Sets)	Y	N	Y
L	Listing 1.21	<Listing 1.21> Adverse Events Listing (Safety Analysis Set)	Y	Y	Y
L	Listing 1.22	<Listing 1.22> ECOG Performance Status (Safety Analysis Set)	Y	Y	Y
L	Listing 1.23	<Listing 1.23> Physical Examinations at Screening (Screening Analysis Set)	Y	N	Y
L	Listing 1.24	<Listing 1.24> Vital Signs (Safety Analysis Set)	Y	Y	Y
L	Listing 1.25	<Listing 1.25> Electrocardiogram Results (Safety Analysis Set)	Y	Y	Y
L	Listing 1.26	<Listing 1.26> Hematology Results and Change from Baseline (Safety Analysis Set	Y	Y	Y
L	Listing 1.27	<Listing 1.27> Chemistry Results and Change from Baseline (Safety Analysis Set)	Y	Y	Y
L	Listing 1.28	<Listing 1.28> Urinalysis Results and Change from Baseline (Safety Analysis Set)	Y	N	Y
L	Listing 1.29	<Listing 1.29> Thyroid functions Summary (Safety Analysis Set)	Y	N	Y
L	Listing 1.30	<Listing 1.30> Serum CA-125 (Safety Analysis Set)	Y	Y	Y

TFL Flag	Master Table Shell ID	Master Shell Title	Cohort A1 and A2 (Y/N)	[redacted]	[redacted]
L	Listing 1.31	<Listing 1.31> Serum Pregnancy testing (Safety Analysis Set)	Y	N	Y
L	Listing 1.32	<Listing 1.32> Coagulation Results and Change from Baseline (Safety Analysis Set)	Y	N	Y

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15.0 Document History

V1.0 – Initial Release

V1.1 – Updates after Protocol amendment 5 dated 10th May 2019

V1.2 – Updates after dry run June 2019

V2.0 – Updates after topline results July 2019

V2.1 – Updates definition for irAE