TITLE PAGE

Protocol Title: A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-033, an Anti-LAG-3 Monoclonal Antibody, Alone and in Combination With an Anti-PD-1 in Patients With Advanced Solid Tumors (CITRINO)

Protocol Number: 213349 (4040-01-001)/Amendment 05 (Version 6.0)

Compound Names: TSR-033 (also known as: encelimab, GSK4074386A)

Dostarlimab (also known as: TSR-042, GSK4057190A)

Study Phase: Phase 1

Sponsor Name and Legal Registered Address:

TESARO, Inc.
1000 Winter Street
Suite 3300
Waltham, MA 02451
+1 339 970 0900

TESARO Bio Netherlands B.V.
Joop Geesinkweg 901
1114AB Amsterdam-Duivendrecht
The Netherlands
+45 31664608

Regulatory Agency Identification Numbers:

Registry	ID
IND	134,547
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Medical Monitor Name and Contact Information: Can be found in the Study Reference Manual

Sponsor Signatory:

Hagop Youssoufian, MD, MSc
Medical Director

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date	Document Number
Amendment 05 (Version 6.0)	23 Feb 2022	TMF-14403236
Amendment 04 (Version 5.0)	29 Jan 2020	TMF-11848538
Amendment 03 (Version 4.0)	24 Jun 2019	RPS-SA-1586848
Amendment 02 (Version 3.0)	02 Jan 2018	RPS-SA-1586671
Amendment 01 (Version 2.0)	19 Jun 2017	RPS-SA-1586272
Original Protocol (Version 1.0)	19 Apr 2017	RPS-SA-1586523

Amendment 05 (23 Feb 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

Amendment 05 is a global protocol amendment to refine the study endpoints and provide operational details for the study after the planned final analysis/database closure. Additional clarifications have also been provided. A description and rationale for all changes is provided in the following Protocol Amendment Summary of Changes table.

Protocol Amendment Summary of Changes

Section # and Name	Description of Change	Brief Rationale
Document headers, Title Page, Sponsor Signatory page (removed), Protocol Amendment Summary of Changes section (new), and throughout	Document headers, Title Page, and Sponsor Signatory page (removed) were updated according to the Sponsor's template; Protocol Amendment Summary of Changes section was added according to the Sponsor's template; editorial revisions were made for consistency with the Sponsor's ways of working and to add clarification and/or remove discrepancies	Editorial changes to align with the Sponsor's standard protocol template and ways of working and for accuracy, clarity, conformity, flow, and typographical error correction

Section # and Name	Description of Change	Brief Rationale
Synopsis→Objectives Section 2.1. Primary Objective, Section 2.2. Secondary Objectives, and Section 2.3. CCI Section 6.3.2. Efficacy Endpoints Section 8.5.2. Secondary Efficacy Parameters	(Primary and Secondary) Provided example parameters to be used for safety/tolerability analyses; provided clarification and example for PK characterization (Secondary) Restricted DOR and DCR analyses by RECIST v1.1 to Part 2 only CCI	To provide additional clarification of example parameters, Part 2 endpoints, and CCI endpoints. CCI
Synopsis → Methodology Section 3.3.3. End of Study and Final Analysis (new section) Section 5.7. Continued Access to Study Treatment After Final Analysis (new section) Section 6.1.12. Collection of Safety Information After Final Analysis (new section) Section 7.1. Schedule of Events (Deleted) Section 9.15. End of Study (section moved to new Section 3.3.3)	Added guidelines for patients who continue treatment after the DCO date of the planned final analysis/database closure	To provide continued treatment options to patients still deriving clinical benefit from treatment when the DCO date is reached

Section # and Name	Description of Change	Brief Rationale
Synopsis→ Pharmacokinetics and Antidrug Antibody Analysis Synopsis→Statistical Methods (Pharmacokinetic Analysis) Section 3.3.1.4. Pharmacokinetics and Antidrug Antibody Assessments Section 6.4.1. Pharmacokinetic Analysis Section 8.1. Study Populations Section 8.3. Pharmacokinetic Analyses	Removed duplicated PK analysis information and clarified existing PK analysis information Updated PK Population definition and added Immunogenicity Population definition	Reduced repeated details of PK analyses for clarity and updated existing details in line with Sponsor's ways of working/for accuracy Updated study population details in line with planned statistical analyses
Synopsis→Investigational Product, Dosage, and Mode of Administration Section 3.1.3.1 Part 1a: TSR-033 Monotherapy (Q2W) Section 5.2. Administration	Revised the text to note that the infusion times provided for TSR-033 and the study treatments in Part 2B are approximate and to remove the 15-minute observation period after an infusion of TSR-033	Per study Protocol Clarification Letter issued 22 June 2021: Approximate infusion timing is deemed sufficient for TSR-033 and all study treatments in Part 2B and the observation period after TSR-033 administration is not required for patient safety
Synopsis→Statistical Methods (Safety Analyses) Section 8.2. Safety Analyses	Removed coagulation, urinalysis, vital signs, and physical examinations from descriptions of statistical analyses	These parameters will not be statistically analyzed
Section 5.1.2. Non-investigational Products	Added a note that biosimilars of bevacizumab are permitted for administration as a substitute for bevacizumab	Per study Protocol Clarification Letter issued 28 June 2021: This clinical practice is deemed allowable

Section # and Name	Description of Change	Brief Rationale
Section 5.3 Dose Modification (Table 2 Dose Modifications for Non-Hematologic Toxicities – Applies to Both Study Drug Components (TSR-033 and Dostarlimab)) Section 5.6.4. Rescue Medications and Supportive Care Guidelines	Added dose modifications and, as appropriate, supportive care guidelines for the following AE categories: adrenal insufficiency; hemophagocytic lymphohistiocytosis; myocarditis; severe exfoliative dermatologic events, severe neurological events; uveitis; and other irARs Reclassified dose modifications for immune-related rash to severe exfoliative dermatologic events and included dose modifications and supportive care guidelines for suspected and confirmed cases of DRESS, SJS, and TEN. Reclassified dose modifications for immune-related encephalitis to include several severe neurological events (myasthenic syndrome/myasthenia gravis, Guillain Barré syndrome, immune-related encephalitis, and transverse myelitis) Made minor clarifying updates to dose modifications for the following AE categories: diarrhea/colitis; AST, ALT, or increased bilirubin; hyperthyroidism; and renal failure or nephritis.	Clarifications, corrections, and program updates. Note, rash and skin reactions are now covered by the new "Other irARs" AE category.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; DCO=data cut-off; DCR=disease control rate; DOR=duration of response; DRESS=drug reaction with eosinophilia and systemic symptoms; irAR=immune-related adverse reaction; CCI Criteria in Solid Tumors; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors.; SJS=Stevens-Johnson syndrome; TEN=toxic epidermal necrolysis.

SYNOPSIS

Name of Sponsor/Company: TESARO, Inc.	
Name of Investigational Product: TSR-033 and dostarlimab	
Name of Active Ingredients: TSR-033 and dostarlimab	
Title of Study: A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-033, an Anti-LAG-3 Monoclonal Antibody, Alone and in Combination With an Anti-PD-1 in Patients With Advanced Solid Tumors	
Study Center(s): Up to 10 sites in Part 1 and up to 20 sites in Part 2	
Studied period (years): Estimated date first patient enrolled: July 2017 Estimated date last patient completed: May 2021	**Phase of development:** 1

Proposal/Rationale: The recognition of tumors by the immune system has been appreciated for multiple decades and has 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. Despite evidence of immune reactivity, tumors are able to grow in the presence of an immune system, suggesting a suboptimal innate immune response.

Emerging research into this inadequate immune response has identified an important family of proteins that play key roles in immune checkpoint pathways, regulatory cascades that ordinarily maintain immune homeostasis, but are co-opted by cancer cells so that they may evade detection and subsequent destruction by the immune system. Prominent proteins within this immune checkpoint family include programmed cell death receptor (PD-1), associated with immune system downregulation and self-tolerance, and lymphocyte activation gene-3 (LAG-3) which is widely associated with exhausted or dysfunctional T cells that show varying degrees of functional impairment in the context of chronic antigen exposure.

To date, PD-1 has been a popular development target of anti-cancer therapies. However, despite favorable response rates observed with these therapies, there remains a large number of patients who derive little clinical benefit from this treatment approach (primary resistance) or suffer a relapse post-treatment (acquired or adaptive immune resistance). To potentially engender a stronger and more durable anti-tumor response, it is thought that a combined treatment approach that targets both PD-1 and LAG-3, complementary immune pathways in intrinsic tumor-cell resistance, may be successful. This belief is bolstered by internal results in the mixed lymphocyte reaction (MLR) assay and efficacy in syngeneic tumor models, which, taken together, provide a rationale for combination therapy with anti-PD-1 and anti-LAG-3 antibodies in cancer.

Two such therapeutic antibodies that target PD-1 and LAG-3 are dostarlimab and TSR-033, respectively. Dostarlimab is a potent humanized immunoglobulin G4 (IgG4) κ monoclonal antibody (mAb) that binds to PD-1 and blocks the interaction between PD-1 and its ligands, programmed cell death ligand-1 (PD-L1) and programmed cell death ligand-2 (PD-L2). The functional antagonist activity of dostarlimab was confirmed in a MLR assay demonstrating enhanced interleukin-2 (IL-2) production upon addition of dostarlimab. Dostarlimab is being studied as monotherapy and in combination in several tumor types to evaluate its safety and tolerability, pharmacokinetics (PK), pharmacodynamics (PDy), and clinical activity in patients with advanced or metastatic solid tumors. TSR-033 is a potent and selective humanized IgG4κ mAb that will undergo dose-limiting studies and safety and tolerability

assessment in patients with advanced or metastatic solid tumors, both alone and in combination with dostarlimab, in Part 1 of this study.

Colorectal cancer (CRC) is one of the most common malignancies worldwide and remains a deadly disease (second most common cause of cancer death in the United States [US]) despite current therapeutic options[1], which include the current standard of care (SOC), chemotherapy with or without anti-angiogenic antibodies or anti-epidermal growth factor receptor (EGFR) antibodies[2] as first- and second-line regimens. In the US, although the incidence rate of CRC in adults aged ≥50 years has declined in recent decades, it has increased by 13% in those aged <50 years. In addition, if the disease progresses to become metastatic CRC (mCRC), it is usually incurable. While colorectal cancers with microsatellite instability are frequently sensitive to check point inhibitor therapy, they make up only about 3% of patients with metastatic disease.[3] Unfortunately, in contrast to many other areas of cancer therapy, the advances achieved with immunotherapy have not yet been replicated in the remaining 97% of patients whose mCRC is microsatellite stable CRC (MSS-CRC). Therefore, MSS-CRC remains an area of great and urgent medical need.

Based on the growing body of evidence from preclinical models, the anti-tumor effects of conventional chemotherapy, used as part of the SOC in CRC, are derived not only from direct tumor cell killing, but also from increased priming of the immune response. This can occur through immunogenic cell death (ICD) which (a) releases a host of antigens/neoantigens and highly immunostimulatory molecules which attract leukocytes and (b) stimulates a type I interferon response which promotes improved antigen presentation and T cell activation. This suggests that chemotherapy can synergize with checkpoint blockade pathways to boost tumor immunosurveillance and improve anti-tumor efficacy. By harnessing the host immune system, immunotherapy may therefore add a complementary and distinct mechanism of action to the currently utilized standard chemotherapeutic and biologic regimens used to treat CRC. Therefore, immunotherapeutic agents warrant further investigation in the clinic to test the hypothesis that the combination of immunotherapy and chemotherapy can synergistically potentiate antitumor responses in patients with MSS-CRC.

Among the cytotoxic chemotherapy choices for CRC, oxaliplatin- and irinotecan-based chemotherapy regimens are most commonly utilized, with clinical outcomes improved by the addition of biologics targeting EGFR or vascular endothelial growth factor (VEGF) or its receptor (VEGFR) in appropriate patients.[4] With regard to oxaliplatin-based regimens, FOLFOX and its variants (ie, modified FOLFOX6 [mFOLFOX6], FOLFOX4) remain popular and are used globally.[5,6] FOLFOX consists of folinic acid (FOL) or leucovorin, 5-fluorouracil (F), and oxaliplatin (OX). mFOLFOX6, given with or without bevacizumab (anti-VEGF mAb), is by far the most commonly used regimen, clinically and in studies, for first-line therapy in CRC.[7] An alternative 3-drug combination is FOLFIRI, which consists of irinotecan (IRI) in addition to FOL and F.[8] This combination can also be given with biologics. While it is generally considered that FOLFOX and FOLFIRI are equivalent regimens, particularly with regard to overall survival (OS)[6], the oxaliplatin-based regimens are utilized more frequently than irinotecan-based regimens in the first-line metastatic setting globally. In the second-line metastatic setting, a number of contemporary trials have established reliable benchmarks for overall response rates and progression-free survival (PFS), as well as OS, with FOLFOX- or FOLFIRI-based regimens. Taken together, the overall response rate with FOLFOX or FOLFIRI chemotherapy with or without biologics appears to be modest in CRC, in the 4% to 15% range.[6,9,10,11,12,13,14]

Beyond second-line therapy, TAS-102, an oral fluoropyrimidine analogue and thymidine phosphorylase inhibitor, has demonstrated an improvement of OS by 1.8 months in patients with refractory disease

versus best supportive care (5.3 versus 7.1 months [HR 0.68, 95% CI 0.58 to 0.81; p<0.001]).[15] In addition, two anti-EGFR monoclonal antibodies, cetuximab and panitumumab, have shown efficacy as monotherapy in the third-line setting in patients with KRAS wild type tumors.[16,17,18] Monotherapy with the anti-angiogenic drug regorafenib has also yielded a modest survival benefit of 1.4 months (6.4 versus 5.0 months [HR ratio 0.77; 95% CI 0.64 to 0.94; one-sided p=0.0052).[19] Finally, immunotherapy with checkpoint inhibitors as monotherapy appears to be active only in patients with microsatellite instability–high (MSI-H) or mismatch repair–deficient (dMMR) CRC.[20,21] Both nivolumab and pembrolizumab are currently approved for MSI-H or dMMR CRC that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. In summary, the current treatment options in first- through fourth-line CRC, their response rates, and the growing knowledge around subtypes of CRC patients, highlight the need for more efficacious therapeutics and support the decision to study TSR-033 and dostarlimab combination therapy in MSS-CRC.

The purpose of Part 2A of the study is to assess the safety and initial efficacy of the combination of TSR-033 and dostarlimab in third- or fourth-line MSS-CRC. Part 2B will assess the safety profile and initial efficacy of mFOLFOX6 (Cohort B1) or FOLFIRI (Cohort B2) plus bevacizumab in combination with TSR-033 and dostarlimab in patients with second-line MSS-CRC who have progressed on a prior first-line regimen.[20]

Objectives:

Primary:

Part 1 (Dose Escalation Cohorts 1a, 1b, and 1c):

- To define the recommended Phase 2 dose (RP2D) and schedule of TSR-033 as monotherapy and in combination with dostarlimab.
- To evaluate the safety and tolerability (eg, number of patients experiencing dose-limiting toxicities [DLTs], adverse events [AEs]/serious adverse events [SAEs]/immune-related adverse events [irAEs], and abnormal hematology/clinical chemistry results) of TSR-033 as monotherapy and in combination with dostarlimab in patients with advanced or metastatic solid tumors.

Part 2A (Dose Expansion Cohort):

- To evaluate the anti-tumor activity of TSR-033 in combination with dostarlimab in anti-PD(L)-1 naïve patients with advanced or metastatic MSS-CRC who have progressed following 2 or 3 prior lines of therapy as measured by objective response rate (ORR) assessed by the Investigators using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Part 2B (Dose Expansion Cohorts B1 and B2):

- B1:
  - To evaluate the safety and tolerability (eg, number of patients experiencing DLTs, AEs/SAEs/irAEs, and abnormal hematology/clinical chemistry results) of TSR-033 and dostarlimab in combination added to mFOLFOX6 and bevacizumab in anti-PD(L)-1 naïve patients with advanced or metastatic MSS-CRC following progression on frontline treatment with FOLFIRI (or variant), with or without biologics.
- B2:
  - To evaluate the safety and tolerability (eg, number of patients experiencing DLTs, AEs/SAEs/irAEs, and abnormal hematology/clinical chemistry results) of TSR-033 and

dostarlimab in combination added to FOLFIRI and bevacizumab in anti-PD(L)-1 naïve patients with advanced or metastatic MSS-CRC following progression on frontline treatment with FOLFOX (or variant), with or without biologics.

Secondary:

In Part 1 and Part 2, unless otherwise specified:

- To characterize the PK (eg, serum concentrations for Part 1 and Part 2 and derived PK parameters for Part 1, as data permit) and immunogenicity of TSR-033 alone, TSR-033 and dostarlimab in combination, and TSR-033 and dostarlimab in combination with chemotherapy and bevacizumab.
- To evaluate additional measures of clinical benefit, including
  - ORR by RECIST v 1.1 *(Part 1)*
  - Duration of response (DOR) by RECIST v1.1 *(Part 2)*
  - Disease control rate (DCR) by RECIST v1.1 *(Part 2)*
- B1:
  - To evaluate the anti-tumor activity of TSR-033 and dostarlimab in combination added to mFOLFOX6 and bevacizumab in patients with advanced or metastatic MSS-CRC following progression on frontline treatment with FOLFIRI, with or without biologics, measured by the ORR as assessed by the Investigator using RECIST v1.1.
- B2:
  - To evaluate the anti-tumor activity of TSR-033 and dostarlimab in combination added to FOLFIRI and bevacizumab in patients with advanced or metastatic MSS-CRC following progression on frontline treatment with FOLFOX (or variant), with or without biologics, measured by the ORR as assessed by the Investigator using RECIST v1.1.

CCI

[redacted]

Methodology:

This is a multi-center, open-label, first-in-human, Phase 1 study evaluating the anti-LAG-3 antibody TSR-033 1) alone, 2) in combination with the anti-PD1 antibody dostarlimab, and 3) in combination with dostarlimab, mFOLFOX6 or FOLFIRI, and bevacizumab. The study will be conducted in 2 parts, with Part 1 consisting of dose escalation to determine the RP2D of TSR-033 as a single agent (Part 1a) and in combination with dostarlimab (Part 1c). RP2D decisions will be based on the occurrence of DLTs or PK/PDy data, as available. Part 1b of the study will aim to better characterize the PK profile of TSR-033 [redacted] These additional patients will not be considered evaluable for dose escalation purposes (ie, not included into the DLT-evaluable population), but will contribute to the overall safety assessment at the dose level being evaluated. These regimens will be evaluated in patients with advanced or metastatic solid tumors who have limited available treatment options as determined by the Investigator.

Part 2A of the study will investigate the anti-tumor activity of TSR-033 and dostarlimab in combination in patients with advanced or metastatic MSS-CRC. While the primary objective of this part of the study is ORR by Investigator assessment, copies of scans will be collected and stored at a repository for potential evaluation.

Part 2B of the study will investigate the safety and anti-tumor activity of TSR-033 and dostarlimab in combination with chemotherapy (Cohort B1: mFOLFOX6, Cohort B2: FOLFIRI) and bevacizumab in patients with advanced or metastatic MSS-CRC. As the primary objective of this part of the study will be safety and tolerability, both Part 2B cohorts will begin by enrolling 6 patients each, with enrollment being paused until the end of the DLT observation period before any further enrollment in this arm. While the secondary objective of this part of the study is ORR by Investigator assessment, copies of scans will be collected and stored at a repository for potential evaluation.

DLT criteria are detailed in the protocol. Toxicities will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

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

The design schema is presented below. The starting doses for Part 2 have been determined based on safety findings in earlier cohorts.

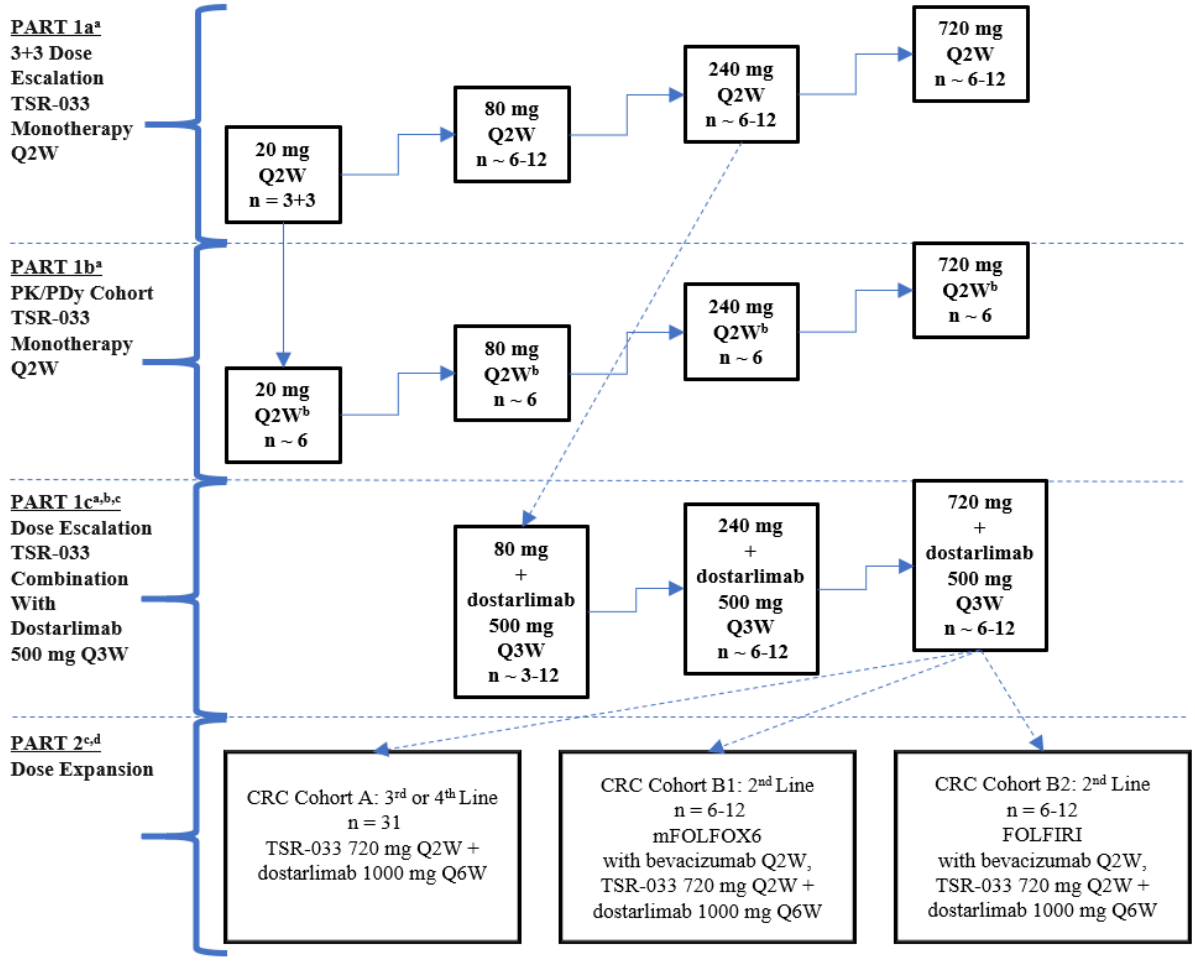
The end of study is defined as the date when the last patient on study has completed his/her last study visit.

The final data cut-off (DCO) date for the study will be defined by the Sponsor and will be communicated to all sites. The DCO date represents the end of data collection for the study and the date on which the clinical study database will be closed to new data.

Patients in Survival Follow-Up at the time of the DCO date will be considered to have completed the study. Patients still on treatment at the time of the DCO date may continue to receive study treatment for up to 2 years unless specific withdrawal criteria are met; patients may also choose to discontinue study treatment at any time. *Note:* Study treatment must be discontinued before the TSR-033 study drug supply expires.

Patients who continue study treatment will be monitored and receive follow-up care in accordance with standard local clinical practice. Assessments will revert to the standard of care at a patient's particular study site, and only SAEs, AEs leading to discontinuation of study treatment, overdoses, and pregnancies will be reported directly to the Sponsor via paper forms. Although the clinical study database will be closed at the time of the DCO date, the study will remain open until all patients discontinue study treatment and the end of study definition (noted above) is reached.

Overall Study Schema



Abbreviations: CRC=colorectal cancer; DLT=dose-limiting toxicity; mg=milligrams; MSS=microsatellite stable; PDy=pharmacodynamics; PK=pharmacokinetics; Q2W=every 2 weeks; Q3W=every 3 weeks; Q6W=every 6 weeks; RP2D=recommended Phase 2 dose.

[a] Approximately 72 patients in Parts 1a, 1b and 1c are expected, but this may increase to approximately 132 patients in total if the Sponsor and Investigators determine that additional safety and/or PK/PDy data are needed to confirm the RP2D for monotherapy. These enrollment numbers could increase if the Sponsor, in consultation with the Investigator, determine that additional cohorts consisting of 6-12 patients are needed to examine additional dose levels. At any dose level, where DLTs were observed in less than ⅓ of patients, in Part 1b, up to 6 additional patients may be enrolled to enable a better characterization of the PK/PDy data in order to confirm the RP2D. These enrollment numbers could further increase if the Sponsor, in consultation with the Investigators determine that an intermediate dose level(s), consisting of approximately 6 patients requires exploration to better understand PK/PDy.

[b] The starting dose of TSR-033 when used in combination with dostarlimab must be one dose level below the highest dose at which <⅓ of 6-12 patients experienced DLTs with single-agent TSR-033.

[c] Doses presented in the schema represent the planned TSR-033 dose levels (subject to change based on safety and/or PK/PDy data). Dostarlimab will be given at a dose of 500 mg (Q3W) in Part 1c and 1000 mg Q6W in Part 2 of the study. These enrollment numbers could increase if the Sponsor, in consultation with the Investigator, determine that additional cohorts consisting of 6-12 patients are needed to examine additional dose levels.

[d] Part 2 will enroll 2 disease-specific cohorts: Cohort A (third- or fourth-line MSS-CRC) and Cohort B (second-line MSS-CRC). The opening of enrollment of the expansion cohorts may not be simultaneous and is dependent on emerging data from ongoing studies.

Number of Patients (Planned):

Approximately 127-187 patients are expected to enroll in this study in total (allowing for replacement of patients and dose expansion).

Part 1: A total of up to approximately 72-132 patients are anticipated:

Part 1a (TSR-033 monotherapy dose escalation): Approximately 30-54 patients

Part 1b (TSR-033 monotherapy PK/[redacted]*):* Approximately 18-30 patients

Part 1c (TSR-033 + dostarlimab combination dose escalation): Approximately 24-48 patients

These enrollment numbers could increase if the Sponsor, in consultation with the Investigator, determines that additional cohorts consisting of 6-12 patients are needed to examine additional dose levels.

Part 2: A total of up to approximately 55 patients are anticipated:

Part 2 Cohort A (TSR-033 + dostarlimab combination dose expansion in anti-PD-1-naïve third- or fourth-line MSS-CRC patients): Approximately 31 patients.

Part 2 Cohort B1 (TSR-033 + dostarlimab combination given with mFOLFOX6 and bevacizumab [SOC] in anti-PD-1-naïve second-line MSS-CRC patients who have progressed on frontline treatment with FOLFIRI, with or without biologics): Approximately 12 patients.

Part 2 Cohort B2 (TSR-033 + dostarlimab combination given with FOLFIRI and bevacizumab [SOC] in anti-PD-1-naïve second-line MSS-CRC patients who have progressed on frontline treatment with FOLFOX [or variant], with or without biologics): Approximately 12 patients.

Should enrollment in Cohort B1 lag, allowance will be made to increase the number of patients enrolled in Cohort B2 after DLT clearance of the first 6 patients, such that an additional 6 to 18 may be enrolled. The total for Part 2B as a whole remains at 24.

Main Patient Selection Criteria

- Key Inclusion Criteria for Patients in Part 1:
  - The patient has any histologically or cytologically confirmed advanced (unresectable) or metastatic solid tumor and has progressive disease (PD) after treatment with available therapies that are known to confer clinical benefit or who are intolerant to treatment.
  - The patient must have an archival tumor tissue sample that is formalin-fixed and paraffin-embedded (FFPE) (blocks preferred over slides) and requested and confirmed available from offsite locations prior to dosing. The quality and quantity of the sample must be confirmed sufficient as per the Study Laboratory Manual. Patients who do not have archival tissue must agree to a new biopsy to obtain fresh tumor tissue prior to dosing.
  - Part 1b (PK/PDy cohort): The patient must have lesions amenable for biopsy and agree to undergo biopsies for fresh tumor tissue prior to treatment, approximately 4 to 6 weeks after initiating study treatment, and, whenever possible, at end of treatment (EOT) and/or the time of PD. Serial biopsies are optional for patients in Part 1a and 1c.

- Key Inclusion Criteria for Patients in Part 2:
  - The patient has any histologically or cytologically confirmed CRC that is metastatic or not amenable to potentially curative resection (advanced), in the opinion of the Investigator.
  - The patient has a primary and/or metastatic tumor(s) that is known to be MSS, as determined locally.
  - The patient must have lesions amenable for biopsy and agree to undergo biopsies for fresh tumor tissue prior to treatment, approximately 4 to 6 weeks after initiating study treatment, and, whenever possible, at EOT and/or the time of PD. If the patient has had a biopsy prior to entering the 28-day screening period, and within approximately 12 weeks of study treatment, that biopsy sample may be accepted as the baseline fresh biopsy. Additionally, submission of sufficient high-quality archival tissue is recommended, if available, to enable a longitudinal analysis of tumor biomarkers.
  - The patient has measurable disease by RECIST v1.1.
  - The patient must have a baseline albumin ≥3.0 g/dL.
- Key Inclusion Criteria for Patients in Part 2A:
  - The patient must have had at least 2, but no more than 3, prior lines of therapy in the advanced or metastatic setting. Adjuvant chemotherapy with radiographic progression >12 months after the last dose will not be considered a line of therapy.
  - The patient has progressed on standard therapies or withdrawn from standard treatment due to unacceptable toxicity. Previous standard treatment must include all of the following: a) fluoropyrimidine, b) oxaliplatin (patients treated with oxaliplatin in adjuvant setting should have progressed after 12 months of completion of adjuvant therapy or they must have been treated with oxaliplatin for metastatic disease), c) irinotecan, d) patients whose disease is known to be RAS-wild-type must have been treated with cetuximab, panitumumab, or other EGFR inhibitor for metastatic disease, and e) bevacizumab and/or another anti-angiogenic agent, and f) previous treatment with regorafenib and/or TAS-102 are allowed in the absence of contraindications and if these agents are available to the patient according to local standards.
  - The time between a patient's last chemotherapy and enrollment must be ≤8 weeks.
- Key Inclusion Criteria for Patients in Part 2B:
  - The patient has received ≤2 prior systemic chemotherapy regimens in any setting (only 1 prior regimen for metastatic disease is permitted).
- Key Inclusion Criteria for Patients in Part 2 Cohort B1:
  - The patient has received first-line combination therapy consisting of bevacizumab or anti-EGFR antibodies with FOLFIRI and has experienced radiographic progression during or after first-line therapy. Radiographic progression >12 months after the last dose of adjuvant therapy will not be considered a line of therapy.

  - mFOLFOX6 therapy with bevacizumab is appropriate for the patient and is recommended by the Investigator.

- Key Inclusion Criteria for Patients in Part 2 Cohort B2:
  - The patient has received first-line combination therapy consisting of bevacizumab or anti-EGFR antibodies with FOLFOX (or variant) and has experienced radiographic progression during or after first-line therapy. Radiographic progression >12 months after the last dose of adjuvant therapy will not be considered a line of therapy.
  - FOLFIRI therapy with bevacizumab is appropriate for the patient and is recommended by the Investigator.
- Key Exclusion Criteria for all Patients:
  - The patient has previously been treated with an anti-LAG-3 antibody.
  - The patient has known uncontrolled central nervous system (CNS) metastases and/or carcinomatous meningitis.
  - The patient has a known concurrent, serious, uncontrolled medical disorder, nonmalignant systemic disease, or active infection requiring systemic therapy, including human immunodeficiency virus (HIV), known active hepatitis B or hepatitis C, active infection, or active autoimmune disease.
  - The patient is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study.
  - The patient has a history of interstitial lung disease.
  - The patient has not recovered (ie, to Grade ≤1 or to baseline) from radiation- and chemotherapy-induced AEs, has received transfusion of blood products (including platelets or red blood cells), or has received administration of colony stimulating factors (including granulocyte colony-stimulating factor [G-CSF], granulocyte macrophage colony-stimulating factor, or recombinant erythropoietin) within 3 weeks prior to the first dose of study drug.
  - The patient is currently participating in an investigational study (therapy or device) or has participated in an investigational study within 4 weeks prior to the first dose of study drug.
  - The 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 the first dose of the drug, whichever is shorter.
  - The patient has not recovered (Grade ≥1) from AEs and/or complications from any major surgery prior to the first dose of study drug.
  - The patient has received a vaccine within 7 days of the first dose of study drug.
  - The patient has known hypersensitivity to TSR-033, dostarlimab (Part 1c and Part 2), or associated excipients.

- Key Exclusion Criteria for Patients in Part 1:
  - Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-LAG-3 agent that resulted in permanent discontinuation due to an AE.
- Key Exclusion Criteria for Patients in Part 2:
  - The patient has been previously treated with an anti-PD-1 or anti-PD-L1 antibody.
- Key Exclusion Criteria for Patients in Part 2B:
  - The patient has known hypersensitivity to bevacizumab, mFOLFOLX6 (Cohort B1) or FOLFIRI (Cohort B2), or associated excipients.
  - The patient experienced PD within 12 months of last dose of adjuvant therapy.

Pharmacokinetics and Antidrug Antibody Analysis

Blood samples for the determination of serum levels of TSR-033 and dostarlimab will be collected from patients in both Part 1 and Part 2. Sampling times for blood PK analysis are detailed in the protocol. All sampling times are relative to the start of the TSR-033 infusion.

In Part 1b, a cohort(s) of up to 6 additional patients may be enrolled in any dose level with DLTs observed in <⅓ of patients to better characterize the PK profile CCI [redacted] CCI [redacted]. In this cohort(s), patients will receive their TSR-033 doses on Day 1, Day 29, and Q2W thereafter. The extended treatment durations in the absence of a Day 15 dose enables better characterization of the terminal phase of the PK profile, which can lead to more accurate calculations of PK parameters (such as terminal half-life [$t_{½}$]). Additionally, this extended treatment interval will provide additional PDy data that may contribute to the determination of the RP2D. The decision regarding which cohort(s) to expand for this evaluation will be determined by the Sponsor and the Investigators.

The serum samples for PK determination will be analyzed using enzyme-linked immunosorbent assay (ELISA).

Antidrug Antibody Analysis

The serum samples for the determination of anti-TSR-033 antibodies and anti-dostarlimab antibodies will be the same samples collected as for PK. Antidrug antibodies (ADAs) will be analyzed using electrochemiluminescence (ECL) with pre-dose samples from all doses collected and terminal phase samples, as appropriate, from the first and sixth doses for Part 1 patients. For all patients, additional samples for ADA determination will be collected upon treatment discontinuation at a safety follow-up (FUP) visit.

CCI [redacted]

CCI

[redacted]

Investigational Product, Dosage, and Mode of Administration:

TSR-033 is a humanized monoclonal IgG4 antibody and will be supplied as a solution in vials containing 80 and 160 mg (20 mg/mL). Throughout the study, TSR-033 will be administered via an approximately 30-minute intravenous (IV) infusion prior to the administration of dostarlimab.

Dostarlimab (previously referred to as TSR-042) is a humanized monoclonal IgG4 antibody and will be supplied as a solution in vials containing 500 mg (50 mg/mL). The 50 mg/mL concentration will only be introduced after approval by health authorities. Dostarlimab will also be administered via a 30 (-5 and +15) minute IV infusion, at every third dose of TSR-033, with a 2-hour observation period on Day 1. Should no infusion reactions (Irs) occur, observation can be reduced to 1 hour, then to 30 minutes.

For the doublet combination, TSR-033 will be administered first, followed by dostarlimab.

In Part 2B, the investigational drugs TSR-033 and dostarlimab will be given in combination with the current SOC in CRC, chemotherapy (mFOLFOX6 [Cohort B1] or FOLFIRI [Cohort B2]) with bevacizumab.

Note: Infusion times described below are approximate.

mFOLFOX6 will be administered at a dose of 85 mg/m^2 of oxaliplatin IV over 2 hours, 400 mg/m^2 of leucovorin IV over 2 hours, followed by 400 mg/m^2 of 5-fluorouracil IV bolus over 2-4 minutes, and a continuous infusion of 2400 mg/m^2 of 5-fluorouracil over 46 hours. This regimen will be repeated every 2 weeks (Q2W). Other variation on the administration schedule may be considered upon discussion with the Medical Monitor.

FOLFIRI will be administered at a dose of 180 mg/m^2 of irinotecan IV over 90 minutes, with 400 mg/m^2 of leucovorin IV over 90 minutes, followed by 400 mg/m^2 of 5-fluorouracil IV bolus, and a continuous infusion of 2400 mg/m^2 5-fluorouracil IV over 46 hours. Other variation on the administration schedule may be considered upon discussion with the Medical Monitor.

For the doublet combination with chemotherapy, the chemotherapy regimen will be administered 2 days prior (Day 1) to the administration of TSR-033 and dostarlimab, which will be given on Day 3 of the dose cycle.

Premedication with anti-emetics and atropine for irinotecan are permitted.

Bevacizumab will be administered at 5 mg/kg on Day 1 prior to chemotherapy and repeated Q2W. Bevacizumab will be administered via a 30 (-5 and +15) minute IV infusion (unless a longer schedule was previously tolerated) with a 15-minute observation period (assuming previously tolerated).

The time for the first total dose for patients receiving the treatment regimen including mFOLFOX6 chemotherapy is 8-9 hours. The time for the first total dose for patients receiving the treatment regimen including FOLFIRI chemotherapy is 7 to 8 hours.

G-CSF can be used according to the American Society of Clinical Oncology guidelines

Oxaliplatin may be discontinued after 6 cycles to reduce the potential for neuropathy should it be deemed appropriate by the Investigator.

Cohort-specific dose and schedule details

Part 1a: TSR-033 will be administered every 14 days ±1 day (Q2W) or every 21 days ±1 day (Q3W).

The planned ascending doses in Part 1a of the study are 20, 80, and 240 mg Q2W. Further dose escalation to 720 mg Q2W may also be assessed in an additional cohort(s) following agreement between the Investigators and Sponsor. Additional cohorts consisting of 6-12 patients to examine additional dose levels may also be explored, if warranted, following agreement between the Investigators and Sponsor.

Part 1b: A cohort(s) of up to 6 additional patients may be enrolled in any dose level with DLTs observed in <⅓ of patients to better characterize the PK profile of TSR-033 CCI [redacted] CCI In this cohort(s) patients will receive their TSR-033 dose on Day 1, Day 29, and continue Q2W thereafter.

Part 1c: TSR-033 will be administered with dostarlimab Q3W throughout Part 1c, and patients will receive dostarlimab at a dose of 500 mg in combination with ascending doses of TSR-033 Q3W. The starting dose of TSR-033 when used in combination with dostarlimab must be one dose level below the highest dose at which <⅓ of patients experienced DLTs with single-agent TSR-033. Planned dose levels of TSR-033 include 80 and 240 mg. A higher dose level of 720 mg Q3W may be explored, if warranted, based on target exposure and safety findings. Additional cohorts consisting of 6-12 patients to examine additional dose levels may also be explored, if warranted, following agreement between the Investigators and Sponsor. Dostarlimab at a dose of 1000 mg may also be tested with the RP2D of TSR-033 given on an every-6-weeks (Q6W) schedule. For all administrations of the combination regimen, TSR-033 will be given first, followed by dostarlimab.

Part 2A: Following completion of the TSR-033 infusion, dostarlimab (1000 mg) will be administered via a 30-minute IV infusion (-5 minute and +15 minute). TSR-033 will be given on a Q2W schedule and dostarlimab on a Q6W schedule. If emerging safety and/or PK data indicate that exploration of a lower TSR-033 dose is warranted, an additional cohort may be opened.

The Pharmacy Manual contains specific instructions for the preparation of each dose and administration of the infusion solution.

Part 2 Cohort B1: Initially, a 6-patient run-in with mFOLFOX6 plus bevacizumab regimen will be tested for safety, with the potential to add 6 additional patients, for a total of 12 patients. The DLT observation period will be from Dose 1, Day 1, through Dose 3, Day 3, prior to the start of infusion. Following the DLT observation period, if ≥2 DLTs are observed, a dose level reduction of TSR-033 to 240 mg can be considered (dose level -1). This dose level would then enroll 6 patients. Alternatively, if

<2 DLTs are observed during the DLT observation period, 6 additional patients may be enrolled at that dose level to confirm safety and collect preliminary efficacy data.

Part 2 Cohort B2: Initially, a 6-patient run-in with FOLFIRI plus bevacizumab regimen will be tested for safety, with the potential to add 6 additional patients, for a total of 12 patients. The DLT observation period will be from Dose 1, Day 1, through Dose 3, Day 3, prior to the start of infusion. Following the DLT observation period, if ≥2 DLTs are observed, a dose level reduction of TSR-033 to 240 mg can be considered (dose level -1). This dose level would then enroll 6 patients. Alternatively, if <2 DLTs are observed during the DLT observation period, 6 additional patients may be enrolled at that dose level to confirm safety and collect preliminary efficacy data. Should enrollment in Cohort B1 fall behind, allowance will be made to increase the number of patients enrolled in Cohort B2 after DLT clearance of the first 6 patients, such that an additional 6 to 18 may be enrolled. The total for Part 2B as a whole remains at 24.

Please refer to the Pharmacy Manual for details on the preparation and administration of the infusion solutions for TSR-033 and dostarlimab.

mFOLFOX6 or FOLFIRI and TSR-033 will be given on a Q2W schedule and dostarlimab on a Q6W schedule.

The full infusion schedule will be as follows:

Part 2 Cohort B1: Infusion times (per dose cycle):

Note: Infusion times described below are approximate.

1. Bevacizumab (Day 1): 30-minute infusion, unless a longer schedule was previously tolerated; 15 minutes observation (assuming previously tolerated).
2. Oxaliplatin with leucovorin (Day 1): 2-hour infusion. (Part of mFOLFOX6 regimen).
3. 5-Fluorouracil (Day 1): 2-4 minutes. (Part of mFOLFOX6 regimen).
4. 5-Fluorouracil (Day 1-3): continuous infusion, 46-hours. (Part of mFOLFOX6 regimen).
5. TSR-033 (Day 3): 30-minute infusion.
6. Dostarlimab (Day 3, every third dose of TSR-033): 30-minute infusion; 2-hour observation for first dose. Should no Irs occur, observation can be reduced to 1 hour for second dose, then to 30 minutes thereafter.

Part 2 Cohort B2: Infusion times (per dose cycle):

Note: Infusion times described below are approximate.

1. Bevacizumab (Day 1): 30-minute infusion, unless a longer schedule was previously tolerated; 15 minutes observation (assuming previously tolerated).
2. Irinotecan with leucovorin (Day 1): 90 minutes. (Part of FOLFIRI regimen).
3. 5-Fluorouracil (Day 1): 2-4 minutes. (Part of FOLFIRI regimen).
4. 5-Fluorouracil (Day1-3): continuous infusion, 46-hours. (Part of FOLFIRI regimen).
5. TSR-033 (Day 3): 30-minute infusion.
6. Dostarlimab (Day 3, every third dose of TSR-033): 30-minute infusion; 2-hour observation for first dose. Should no Irs occur, observation can be reduced to 1 hour for second dose, then to 30 minutes thereafter.

Part 2B Dosing Schema:

Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11[a]
Dose 1[b]		Dose 2[b]		Dose 3[b]		Dose 4[b]		Dose 5[b]		Dose 6[b]
Bevacizumab		Bevacizumab		Bevacizumab		Bevacizumab		Bevacizumab		Bevacizumab
mFOLFOX6[c] or FOLFIRI[d]		mFOLFOX6[c] or FOLFIRI[d]		mFOLFOX6[c] or FOLFIRI[d]		mFOLFOX6[c] or FOLFIRI[d]		mFOLFOX6[c] or FOLFIRI[d]		mFOLFOX6[c] or FOLFIRI[d]
TSR-033 (Day 3)		TSR-033 (Day 3)		TSR-033 (Day 3)		TSR-033 (Day 3)		TSR-033 (Day 3)		TSR-033 (Day 3)
Dostarlimab (Day 3)						Dostarlimab (Day 3)				

Abbreviation: Wk=week.

[a] This treatment regimen may be continued for so long as the patient is, in the opinion of the Investigator, benefiting from treatment.

[b] Drug administered on Day 1 unless otherwise noted.

[c] Cohort B1.

[d] Cohort B2.

Duration of Treatment:

Planned Study Conduct Duration: Approximately 42 months (time from first patient enrolled until study cut-off [when responder or discontinuation status for all patients is known]).

Planned Study Treatment Duration: Enrolled patients may continue study treatment for up to 2 years or until PD, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued study treatment beyond 2 years may be considered following discussion between the Sponsor and Investigator.

Criteria for Evaluation:

Pharmacokinetics:

Serum samples for PK determination will be collected prior to, during, and after treatment with TSR-033 alone or in combination with dostarlimab, and the dual immunotherapy regimen in combination with chemotherapy and bevacizumab as described in the protocol.

Serum samples for ADA assessments will be collected prior to, during, and after treatment with TSR-033 alone or in combination with dostarlimab, and the dual immunotherapy regimen in combination with chemotherapy and bevacizumab. Results of ADA assays (screening, confirmation, and neutralizing antibody [NAb]) will be correlated with clinical activity, PK, as well as safety assessments.

Pharmacodynamics:

During Part 1 and Part 2, blood cells may be assessed for LAG-3 receptor occupancy according to the schedule detailed in the protocol.

In addition, these analyses may include, but are not limited to, assessing changes in circulating immune cells, serum cytokines, ctDNA, and soluble LAG-3 to better characterize the clinical activity of TSR-033 and may be considered for selection of the RP2D.

Safety:

Safety assessments conducted throughout the treatment period include symptom-directed physical examinations, AE and DLT assessment, vital signs, electrocardiograms (ECGs), ECOG PS, and clinical laboratory assessments, including complete blood count (CBC) with 5-part differential, coagulation factors, chemistry, thyroid panel (ie, thyroid-stimulating hormone [TSH], triiodothyronine [T3], free

triiodothyronine [FT3], thyroxine [T4], free thyroxine [FT4], or equivalent tests, where applicable), urinalysis, and pregnancy testing.

Statistical Methods:

All descriptive statistical analyses will be performed using the most recently released and available SAS statistical software, unless otherwise noted. For categorical variables, the number and percent of each category within a parameter will be calculated. For continuous variables, the sample size (n), mean, median, and standard deviation, as well as the minimum and maximum values, will be presented. Missing data will not be imputed unless otherwise stated. There will be a detailed description of patient disposition; patient demographics and baseline characteristics will be summarized.

No formal interim analysis is planned for this study. However, a review of safety data and available preliminary PK data will be conducted by the Sponsor and Investigators following completion of the DLT observations periods in Part 1a, Part 1c, and Part 2B. Determination of the RP2D will be based on review of safety, PK, and PDy data. A statistical analysis plan (SAP) will fully describe the planned analyses for this trial. All analyses will be performed for any patient that received any amount of study drug. All analyses for efficacy will use Dose 1, Day 1 as the start time.

Sample Size

Ascending doses of TSR-033 in Part 1a and in combination with dostarlimab in Part 1c will be evaluated to identify the RP2Ds. The actual number of patients accrued during this phase will be determined largely by the safety and PK findings observed during the course of their treatment. RP2D decisions for Part 1a and Part 1c will be based on a minimum of 6 patients for each regimen. Patients in Part 1b (PK/PDy cohort) will not be considered evaluable for dose escalation purposes (ie, not included into the DLT-evaluable population) but will contribute to the overall safety assessment at the dose level being evaluated. It is expected that up to approximately 132 patients will be enrolled in Part 1 as follows:

Part 1a (TSR-033 monotherapy dose escalation): Approximately 30-54 patients

Part 1b (TSR-033 PK/[redacted]: Approximately 18-30 patients

Part 1c (TSR-033 + dostarlimab dose escalation): Approximately 24-48 patients

A total of up to approximately 55 patients are anticipated in the 2 planned expansion cohorts in Part 2. In each expansion cohort, an exact single stage design will be used. Each cohort is designed with a one-sided type I error rate of 10% and a power of 80%.

Part 2A (TSR-033 + dostarlimab combination dose expansion in anti-PD-1-naïve third- or fourth-line MSS-CRC patients): A null hypothesis of ORR 10% will be tested against an alternative hypothesis of ORR 25%. The trial is designed using a one-sided exact test that achieves a minimum of 80% power at alpha level of 0.1. A sample size of 31 will provide an attained power of 82.4% and an attained type-1 error of 0.083. The null hypothesis will be rejected if 6 or more responses are observed in the 31 patients.

Part 2B (TSR-033 + dostarlimab combination given in with mFOLFOX6 or FOLFIRI and bevacizumab [SOC] in anti-PD-1-naïve second-line MSS-CRC patients) A null hypothesis of ORR 20% will be tested against an alternative hypothesis of ORR 40%. The trial is designed using a one-sided exact test that achieves a minimum of 80% power at alpha level of 0.1. A sample size of 24 will provide an attained power of 80.8% and an attained type-1 error of 0.089. The null hypothesis will be rejected if 8 or more responses are observed in the 24 patients.

Pharmacokinetic Analysis

Noncompartmental methods will be used to evaluate the PK characteristics of TSR-033 in Part 1a and Part 1b and TSR-033 and dostarlimab in Part 1c and Part 2, as appropriate. PK parameters such as maximum concentration (C_{max}), time at maximum concentration (T_{max}), area under the concentration-time curve (AUC), $t_{½}$, volume of distribution at steady state (V_{ss}), and clearance (CL) may be derived from serum concentrations using actual sampling times, as data permit. Concentration-time data and PK parameters will be listed and summarized descriptively by cohort, dose level, and dose number. Concentration data may be included in a population PK analysis, the results of which will be reported separately.

Safety Analyses

AEs, concomitant medication, and results from physical examination will be listed.

AEs will also be coded with the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized per system organ class and preferred term.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (September 2016 or later version). A dictionary listing of all unique concomitant medications used in the study will be provided.

All hematology, blood chemistry, and ECG results will be listed per patient for each assessment, and descriptive statistics will be tabulated for select criteria. Serum will be evaluated for the presence of ADAs.

Efficacy Analyses

ORR will be calculated for Part 2 and will be summarized and presented in tables and listings. 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. Time-to-event analyses will be performed using Kaplan-Meier (KM) methods.[22]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation	Definition
ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BP	blood pressure (resting)
CBC	complete blood count
CEA	carcinoembryonic antigen
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
$CrCL/C_{cr}$	creatinine clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CIOMS	Council for International Organizations of Medical Sciences
DCR	disease control rate
DCO	data cut-off
DLT	dose-limiting toxicity
dMMR	mismatch repair-deficient
DOR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms

Abbreviation	Definition
ECG	electrocardiogram
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EOT	end of treatment
F	5-fluorouracil
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FOL	folinic acid (leucovorin)
FT3	free triiodothyronine
FT4	free thyroxine
FUP	follow-up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
G-CSF	granulocyte-colony stimulating factor
GLP	Good Laboratory Practice
Hb	hemoglobin
HbsAg	hepatitis B surface antigen
HCV RNA	hepatitis C virus ribonucleic acid
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICD	immunogenic cell death
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
IL-2	interleukin-2
INR	international normalized ratio
IR	infusion reaction

Abbreviation	Definition
irAE	immune-related adverse event
irAR	immune-related adverse reaction
IRB	Institutional Review Board
irCR	immune-related complete response
IRI	irinotecan
irPD	immune-related progressive disease
irPR	immune-related partial response
CCI	[redacted]
irSD	immune-related stable disease
IV	intravenous(ly)
KM	Kaplan-Meier
LAG-3	lymphocyte activation gene-3
mAb	monoclonal antibody
MAD	maximum administered dose
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MLR	mixed lymphocyte reaction
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
MSS	microsatellite stable
MTD	maximum tolerated dose
NAb	neutralizing antibody
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OX	oxaliplatin
PD	progressive disease
PD-1	programmed cell death-1 receptor
PD-L1	programmed death ligand-1
PD-L2	programmed death ligand-2

Abbreviation	Definition
PDy	pharmacodynamic(s)
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	per os (by mouth)
PR	partial response
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SJS	Stevens-Johnson syndrome
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal half-life
T1DM	type 1 diabetes mellitus
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TIL	tumor-infiltrating lymphocytes
TIM-3	T-cell immunoglobulin and mucin-domain containing-3 receptor
T_{max}	time at maximum concentration
TRAE	treatment-related adverse event
TSH	thyroid-stimulating hormone

Abbreviation	Definition
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
V_{ss}	volume of distribution at steady state
WHO	World Health Organization
WOCBP	women of child bearing potential

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. Despite evidence of immune reactivity, tumors are able to grow in the presence of an immune system, suggesting a suboptimal immune response.

Emerging research into this inadequate immune response has identified an important family of proteins that play key roles in immune checkpoint pathways, regulatory cascades that ordinarily maintain immune homeostasis, but are co-opted by cancer cells so that they may evade detection and subsequent destruction by the immune system. Prominent proteins within this immune checkpoint family include lymphocyte activation gene (LAG-3) and programmed cell death-1 receptor (PD-1), which are widely associated with exhausted or dysfunctional T cells that show varying degrees of functional impairment in the context of chronic antigen exposure and are associated with immune system downregulation and self-tolerance.

1.1.1. Lymphocyte Activation Gene-3

LAG-3 was first identified on activated T cells and a subset of natural killer cells. Its engagement on T cells results in the attenuation of T cell signaling and reduced effector function, and it has thus been implicated in limiting anti-tumor immunity.[23,24] LAG-3, along with other co-inhibitory receptors (eg, PD-1, T-cell immunoglobulin and mucin-domain containing-3 receptor [TIM-3]) is widely associated with exhausted or dysfunctional T cells, which show varying degrees of functional impairment in the context of chronic antigen exposure.[25]

1.1.1.1. TSR-033

TSR-033 is a potent and selective humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4) κ isotype that binds to human and cynomolgus monkey LAG-3 with high affinity and blocks the binding of LAG-3 to major histocompatibility complex (MHC) Class II-expressing Daudi cells. Functionally, as a single agent, TSR-033 enhances T cell activation (as determined by interleukin-2 [IL-2]) in a mixed lymphocyte reaction (MLR) with a half-maximal effective concentration of approximately 2 nM. Furthermore, the combination of TSR-033 with an anti-PD-1 antibody increased T cell activation in this assay, resulting in a 5- to 10-fold increase in potency of the combination versus TSR-033 alone. These data, together with other nonclinical data, support the evaluation of TSR-033 as a monotherapy, and in combination with anti-PD-1, in cancer patients.

Please refer to the current version of the Tesaro TSR-033 Investigator's Brochure (IB) for further nonclinical and clinical details about this investigational product.

1.1.2. Programmed Cell Death-1 Protein

Initial exploration of T cell activation in chronic viral models suggested that chronic viral infections led to a state of T cell hypo-responsiveness, termed T cell exhaustion, and involved

immune inhibitory receptors expressed by T cells.[25,26] One of the proteins shown to be mediating T cell exhaustion in chronic viral models and subsequently tumor models was PD-1. The discovery and characterization of PD-1 revealed that PD-1 limits T cell activation through binding to programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2) and limiting tyrosine kinase signaling from the T cell antigen receptor and co-stimulatory receptors.[27,28]

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.[29] These data led to the hypothesis that PD-1/PD-L1 may be exploited to subvert the anti-tumor immune response. Nonclinical models where PD-1 signaling was blocked or deficient (PD-1 knockout mice) demonstrated improved immune-mediated tumor control.[30,31] 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 nonclinical 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 higher compared to past immunotherapeutic approaches.[32] Activity was demonstrated in tumors known to be responsive to immunotherapy, such as melanoma and renal cell carcinoma (RCC), as well as lung tumors which were traditionally insensitive to immunotherapy, like 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 melanoma, RCC, NSCLC and other cancer types have yielded positive data with 2 different antibodies targeting PD-1, nivolumab and pembrolizumab, demonstrating improved response rates and survival.[33-38] Based on the clinical activity and manageable safety profile reported in these pioneering studies, nivolumab and pembrolizumab both have received approval by the US Food and Drug Administration (FDA) and European Medicinal Agency (EMA) in a number of indications (refer to current labels). Although nivolumab and pembrolizumab are distinct antibodies, the safety profiles are very similar across therapies and across tumor types demonstrating that the targeting of PD-1 was well-tolerated with manageable immune-related adverse events (irAEs) being the most noteworthy.

1.1.2.1. Dostarlimab

Dostarlimab is a potent humanized mAb of the IgG4κ isotype that binds to PD-1 and blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. The functional antagonist activity of dostarlimab was confirmed in a MLR assay demonstrating enhanced IL-2 production upon addition of dostarlimab.

Dostarlimab is being studied as monotherapy and in combination in several tumor types to evaluate its safety and tolerability, pharmacokinetics (PK), pharmacodynamics (PDy), and clinical activity in patients with advanced or metastatic solid tumors.

Dose escalation of dostarlimab as monotherapy continued to a maximally administered dose of 10 mg/kg every 2 weeks (Q2W); no dose-limiting toxicities (DLTs) were observed and a maximum tolerated dose (MTD) was not reached. Flat doses of 500 mg every 3 weeks (Q3W) and 1000 mg every 6 weeks (Q6W) were also evaluated for safety in cohorts of 6 patients each

and were found to be safe for currently ongoing assessment in the Part 2 expansion cohorts as no DLTs were observed. The 1000 mg flat dose will also be used in combination with TSR-033 in Part 2 of this study.

The current safety data for patients receiving dostarlimab monotherapy report the most commonly observed (>15%) adverse events (AEs) as: fatigue, nausea, diarrhea, decreased appetite, anemia, constipation, and vomiting. These AEs are typical of and seen in patients receiving other similar drugs in this class (PD-1 inhibitors).

CCI

Please refer to the current version of the Tesaro dostarlimab IB for further nonclinical and clinical details about this investigational product.

1.2. Rationale for Evaluating TSR-033 as Combination Therapy

1.2.1. TSR-033 and Dostarlimab

LAG-3 is expressed on TILs across a wide range of tumor types, such as colorectal, breast, ovarian, prostatic, renal cancers, NSCLC, and melanoma.[39-43] LAG-3 is frequently co-expressed with PD-1 on TILs, and dual blockade of PD-1 and LAG-3 enhances CD8 effector function ex vivo in patient TILs and potentiates anti-tumor immunity in preclinical models of ovarian cancer, colon carcinoma, and fibrosarcoma.[44,45]

To date, clinical data are available for one study investigating anti-LAG-3 and anti-PD-1 antibodies in combination.[46] The safety and PK of the anti-LAG-3 antibody BMS-986016 was evaluated as a single agent in 23 patients with solid tumors, at the following dose levels: 20 mg, 80 mg, 240 mg, or 800 mg. Fifty-seven patients were treated with BMS-986016 in combination with nivolumab (Opdivo®) at the following dose levels (BMS-986016 dose/nivolumab dose): 20/80 mg, 20/240 mg, 80/240 mg, or 240/240 mg. While the MTD was not achieved, and dose escalation of the combination continues, immune-mediated DLTs typically associated with checkpoint inhibitors were observed. Of the 23 patients treated with monotherapy, 3 patients were reported with Grade ≥3 AEs; these included elevated lipase (2 patients) and maculopapular

rash (1 patient). Of the 57 patients treated with BMS-986016 + nivolumab, 7 patients reported AEs Grade ≥3. These included Grade 3 or 4 elevated lipase, elevated amylase, colitis, dehydration, dyspnea, aseptic meningitis, mucosal inflammation, elevated troponin, and ventricular fibrillation (in one patient each). One patient treated at a dose of BMS-986016 240 mg + nivolumab 240 mg experienced Grade 5 myocarditis; this patient had a history of heart disease. Preliminary evidence of clinical benefit was observed in patients with melanoma, NSCLC, cervical cancer, anal cancer, and cholangiocarcinoma.

Despite favorable response rates observed with PD-1/PD-L1 checkpoint inhibitors, there remain large numbers of patients who derive little clinical benefit from such therapies (primary resistance) or suffer a relapse (acquired or adaptive immune resistance).[47] LAG-3 is implicated in tumor cell extrinsic resistance mechanisms, suggesting that targeting this pathway, in addition to PD-1, may engender a stronger and more durable anti-tumor response.[47] These data are consistent with our own results in the MLR assay and efficacy in syngeneic tumor models and, taken together, provide a rationale for combination therapy with anti-PD-1 and anti-LAG-3 antibodies in cancer.

1.2.2. TSR-033 and Chemotherapy with Anti-Growth Factor Antibodies

Based on a growing body of evidence in preclinical models, the anti-tumor effects of conventional chemotherapy derive not only from direct tumor cell killing, but also from increased priming of the immune response.[48] This can occur through immunogenic cell death (ICD) which (a) releases a host of antigens/neoantigens as well as highly immunostimulatory molecules which attract leukocytes and (b) stimulation of a type I interferon response which promotes improved antigen presentation and T cell activation.[49] Chemotherapy can thus synergize with checkpoint blockade to boost tumor immunosurveillance and improve anti-tumor efficacy. Also harnessing the host immune system, immunotherapy may add a complementary and distinct mechanism of action to the currently utilized standard chemotherapeutic and biologic regimens used to treat many forms of cancer. Therefore, immunotherapeutic agents warrant further investigation in the clinic to test the hypothesis that the combination of immunotherapy and chemotherapy can synergistically potentiate antitumor responses. This idea will be studied in Part 2 of the current protocol, investigating the efficacy of TSR-033 and dostarlimab therapy in combination with chemotherapy in patients with advanced or metastatic colorectal cancer (CRC) (see Section 1.2.3).

1.2.3. Rationale for Selection of Expansion Cohorts

CRC is one of the most common malignancies worldwide and remains a deadly disease (second most common cause of cancer death in the United States [US]) despite current therapeutic options[1], which include the current standard of care (SOC), chemotherapy with or without anti-angiogenic antibodies or anti-epidermal growth factor receptor (EGFR) antibodies[2] as first- and second-line regimens. In the US, although the incidence rate of CRC in adults aged ≥50 years has declined in recent decades, it has increased by 13% in those aged <50 years. In addition, if the disease progresses to become metastatic CRC (mCRC), it is usually incurable. While colorectal cancers with microsatellite instability are frequently are frequently sensitive to check point inhibitor therapy, they make up only about 3% of patients with metastatic disease.[3] Unfortunately, in contrast to many other areas of cancer therapy, the advances achieved with

immunotherapy have not yet been replicated in the remaining 97% of patients whose mCRC is microsatellite stable CRC (MSS-CRC). Therefore, MSS-CRC remains an area of great and urgent medical need.

Among the cytotoxic chemotherapy choices for CRC, oxaliplatin- and irinotecan-based chemotherapy regimens are most commonly utilized, with clinical outcomes improved by the addition of biologics targeting EGFR or vascular endothelial growth factor (VEGF) or its receptor (VEGFR) in appropriate patients.[4] With regard to oxaliplatin-based regimens, FOLFOX and its variants (ie, modified FOLFOX6 [mFOLFOX6], FOLFOX4) remain popular and are used globally.[5,6] FOLFOX consists of folinic acid (FOL) or leucovorin, 5-fluorouracil (F), and oxaliplatin (OX). mFOLFOX6, given with or without bevacizumab (anti-VEGF mAb), is by far the most commonly used regimen, clinically and in studies, for first-line therapy in CRC.[7] An alternative 3-drug combination is FOLFIRI, which consists of irinotecan (IRI) in addition to FOL and F.[8] This combination can also be given with biologics. While it is generally considered that FOLFOX and FOLFIRI are equivalent regimens, particularly with regard to overall survival (OS)[6], the oxaliplatin-based regimens are utilized more frequently than irinotecan-based regimens in the first-line metastatic setting globally. In the second-line metastatic setting, a number of contemporary trials have established reliable benchmarks for overall response rates and progression-free survival (PFS), as well as OS, with FOLFOX- or FOLFIRI-based regimens. Taken together, the overall response rate with FOLFOX or FOLFIRI chemotherapy with or without biologics appears to be modest in CRC, in the 4% to 15% range.[6,9,10,11,12,13,14]

Beyond second-line therapy, TAS-102, an oral fluoropyrimidine analogue and thymidine phosphorylase inhibitor, has demonstrated an improvement of OS by 1.8 months in patients with refractory disease versus best supportive care (5.3 versus 7.1 months [HR 0.68, 95% CI 0.58 to 0.81; $p<0.001$]).[15] In addition, two anti-EGFR monoclonal antibodies, cetuximab and panitumumab, have shown efficacy as monotherapy in the third-line setting in patients with KRAS wild type tumors.[16,17,18] Monotherapy with the anti-angiogenic drug regorafenib has also yielded a modest survival benefit of 1.4 months (6.4 versus 5.0 months [HR ratio 0.77; 95% CI 0.64 to 0.94; one-sided $p=0.0052$).[19] Finally, immunotherapy with checkpoint inhibitors as monotherapy appears to be active only in patients with microsatellite instability–high (MSI-H) or mismatch repair–deficient (dMMR) CRC.[20,21] Both nivolumab and pembrolizumab are currently approved for MSI-H or dMMR CRC that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. In summary, the current treatment options in first- through fourth-line CRC, their response rates, and the growing knowledge around subtypes of CRC patients, highlight the need for more efficacious therapeutics and support the decision to study TSR-033 and dostarlimab combination therapy in MSS-CRC.

The purpose of Part 2A of the study is to assess the safety and initial efficacy of the combination of TSR-033 and dostarlimab in third- or fourth-line MSS-CRC. Part 2B will assess the safety profile and initial efficacy of mFOLFOX6 (Cohort B1) or FOLFIRI (Cohort B2) plus bevacizumab in combination with TSR-033 and dostarlimab in patients with second-line MSS-CRC who have progressed on a prior first-line regimen.[20] The second part of the study will explore anti-tumor activity in the pre-specified tumor types and confirm the safety and tolerability of TSR-033 in combination with dostarlimab and/or chemotherapy.

2. TRIAL OBJECTIVES

2.1. Primary Objective

2.1.1. Part 1: Dose Escalation Cohorts (1a, 1b, and 1c)

- To define the RP2D and schedule of TSR-033 as monotherapy (1a, 1b) and in combination with dostarlimab (1c).
- To evaluate the safety and tolerability (eg, number of patients experiencing DLTs, AEs/serious adverse events [SAEs]/irAEs, and abnormal hematology/clinical chemistry results) of TSR-033 as monotherapy (1a, 1b) and in combination with dostarlimab (1c) in patients with advanced or metastatic solid tumors

2.1.2. Part 2A: CRC Dose Expansion Cohort A

- To evaluate the anti-tumor activity of TSR-033 in combination with dostarlimab in anti-PD(L)-1 naïve patients with advanced or metastatic MSS-CRC who have progressed following 2 or 3 prior lines of therapy as measured by objective response rate (ORR) assessed by the Investigators using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

2.1.3. Part 2B: CRC Dose Expansion Cohorts B1 and B2

- B1:
  - To evaluate the safety and tolerability (eg, number of patients experiencing DLTs, AEs/SAEs/irAEs, and abnormal hematology/clinical chemistry results) of TSR-033 and dostarlimab in combination added to mFOLFOX6 and bevacizumab in anti-PD-1-naïve patients with advanced or metastatic MSS-CRC following progression on frontline treatment with FOLFIRI (or variant), with or without biologics.
- B2:
  - To evaluate the safety and tolerability (eg, number of patients experiencing DLTs, AEs/SAEs/irAEs, and abnormal hematology/clinical chemistry results) of TSR-033 and dostarlimab in combination added to FOLFIRI and bevacizumab in anti-PD-1-naïve patients with advanced or metastatic MSS-CRC following progression on frontline treatment with FOLFOX (or variant), with or without biologics.

2.2. Secondary Objectives

In Part 1 and Part 2, unless otherwise specified:

- To characterize the PK (eg, serum concentrations for Part 1 and Part 2 and derived PK parameters for Part 1, as data permit) and immunogenicity of TSR-033 alone, TSR-033 and dostarlimab in combination, and TSR-033 and dostarlimab in combination with chemotherapy and bevacizumab.

- To evaluate additional measures of clinical benefit, including
  - ORR by RECIST v1.1 *(Part 1)*
  - Duration of response (DOR) by RECIST v1.1 *(Part 2)*
  - Disease control rate (DCR) by RECIST v1.1 *(Part 2)*
- B1:
  - To evaluate the anti-tumor activity of TSR-033 and dostarlimab added to mFOLFOX6 and bevacizumab in patients with advanced or metastatic MSS-CRC following progression on frontline treatment with FOLFIRI, with or without biologics, measured by the ORR as assessed by the Investigator using RECIST v1.1.
- B2:
  - To evaluate the anti-tumor activity of TSR-033 and dostarlimab added to FOLFIRI and bevacizumab in patients with advanced or metastatic MSS-CRC following progression on frontline treatment with FOLFOX (or variant), with or without biologics, measured by the ORR as assessed by the Investigator using RECIST v1.1.

3. INVESTIGATIONAL PLAN

This is a multi-center, open-label, first-in-human, Phase 1 study evaluating the anti-LAG-3 antibody TSR-033 alone, in combination with the anti-PD1 antibody dostarlimab, and the combination of TSR-033 and dostarlimab with mFOLFOX6 or FOLFIRI and bevacizumab. The study will be conducted in 2 parts, with Part 1 consisting of dose escalation to determine the RP2D of TSR-033 as a single agent (Part 1a) and in combination with dostarlimab (Part 1c). RP2D decisions will be based on the occurrence of DLTs or PK/PDy data, as available. Part 1b of the study will aim to better characterize the PK profile of TSR-033 CCI CCI These additional patients will not be considered evaluable for dose escalation purposes (ie, not included into the DLT-evaluable population) but will contribute to the overall safety assessment at the dose level being evaluated. In Part 2, these regimens will be evaluated in patients with advanced or metastatic MSS-CRC who have limited available treatment options as determined by the Investigator.

Part 2A of the study will investigate the anti-tumor activity of TSR-033 and dostarlimab in combination in patients with advanced or metastatic MSS-CRC. While the primary objective of this part of the study is ORR by Investigator assessment, copies of scans will be collected and stored at a repository for potential evaluation.

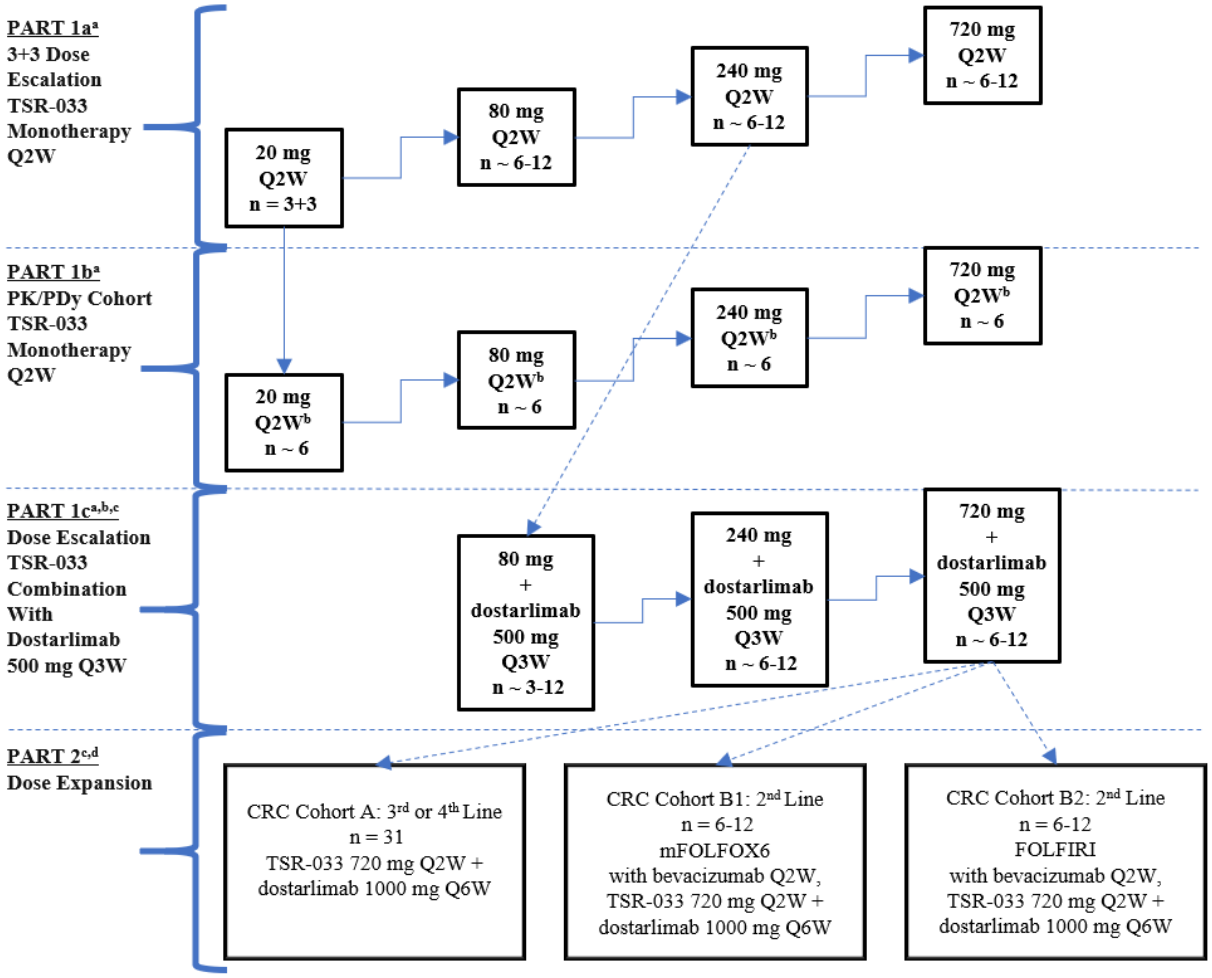
Part 2B of the study will investigate the safety and anti-tumor activity of TSR-033 and dostarlimab in combination with chemotherapy (Cohort B1: mFOLFOX6, Cohort B2: FOLFIRI) and bevacizumab in patients with advanced or metastatic MSS-CRC. As the primary objective of this part of the study will be safety, both Part 2B Cohorts will begin by enrolling 6 patients each, with enrollment being paused until the end of the DLT observation period before any further enrollment in this arm. While the secondary objective of this part of the study is ORR by Investigator assessment, copies of scans will be collected and stored at a repository for potential evaluation.

DLT criteria are detailed in Section 3.1.1. Toxicities will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 for Part 1a, 1c, and Part 2B.

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

The design schema presented below (starting doses for Part 1b, Part 1c, and Part 2 are contingent on safety findings in earlier cohorts).

Figure 1: Overall Study Schema



Abbreviations: CRC=colorectal cancer; DLT=dose-limiting toxicity; mg=milligrams; MSS=microsatellite stable; PDy=pharmacodynamics; PK=pharmacokinetics; Q2W=every 2 weeks; Q3W=every 3 weeks; Q6W=every 6 weeks; RP2D=recommended Phase 2 dose.

[a] Approximately 72 patients in Parts 1a, 1b and 1c are expected, but this may increase to approximately 132 patients in total if the Sponsor and Investigators determine that additional safety and/or PK/PDy data are needed to confirm the RP2D for monotherapy. These enrollment numbers could increase if the Sponsor, in consultation with the Investigator, determine that additional cohorts consisting of 6-12 patients are needed to examine additional dose levels. At any dose level, where DLTs were observed in less than ⅓ of patients, in Part 1b, up to 6 additional patients may be enrolled to enable a better characterization of the PK/PDy data in order to confirm the RP2D. These enrollment numbers could further increase if the Sponsor, in consultation with the Investigators determine that an intermediate dose level(s), consisting of approximately 6 patients requires exploration to better understand PK/PDy.

[b] The starting dose of TSR-033 when used in combination with dostarlimab must be one dose level below the highest dose at which <⅓ of 6-12 patients experienced DLTs with single-agent TSR-033.

[c] Doses presented in the schema represent the planned TSR-033 dose levels (subject to change based on safety and/or PK/PDy data). dostarlimab will be given at a dose of 500 mg (Q3W) in Part 1c and 1000 mg Q6W in Part 2 of the study. These enrollment numbers could increase if the Sponsor, in consultation with the Investigator, determine that additional cohorts consisting of 6-12 patients are needed to examine additional dose levels.

[d] Part 2 will enroll 2 disease-specific cohorts: Cohort A (third- or fourth-line MSS-CRC) and Cohort B (second-line MSS-CRC). The opening of enrollment of the expansion cohorts may not be simultaneous and is dependent on emerging data from ongoing studies.

3.1.1. DLT Criteria

DLT Criteria for assessments in Part 1a, 1c, and 2B (unless noted) include treatment-related adverse events (TRAEs) as detailed below:

- 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 or 3 colitis or diarrhea that persists without resolution to Grade ≤1 for ≥7 days despite adequate immune suppressive therapy.
- Grade 3 or 4 irAE without resolution to Grade ≤1 or baseline within 8 days despite adequate immune suppressive therapy per Section 5.6.4 and Table 3.
- Any Grade clinically significant irAE (eg, myocarditis, encephalitis) requiring treatment discontinuation.
- Any other Grade ≥3 non-hematologic clinical (non-laboratory) toxicity excluding:
  - Nausea and vomiting resolving to Grade ≤1 within 48 hours.
  - Grade 3 fatigue with duration <7 days.
  - In Part 2B, events deemed by the Investigator to be related to the chemotherapeutic or biologic agents administered as SOC alongside the study drugs.
- Any clinically-significant Grade ≥3 non-hematologic laboratory abnormality.
- Any clinically-significant 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 requiring blood transfusion.
- Any death that is not clearly attributed to the underlying disease or extraneous causes.

Treatment-related toxicity is defined as an AE that is not clearly attributable to other causes (eg, PD or a pre-existing medical condition). Toxicities will be assessed according to the CTCAE v5.0. If multiple toxicities occur, the presence of DLT will be graded based on the most severe toxicity observed.

At the end of the respective DLT observation periods, 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 DLTs may be considered for continuing treatment given the appropriate clinical context (eg, may continue treatment if a transient Grade 3 laboratory abnormality is asymptomatic and otherwise unremarkable) following discussion between the Investigators and Sponsor.

For the purposes of dose escalation decision or determining RP2D, all safety data from the dose escalation cohorts, including all irAEs, regardless of severity occurrence within the DLT window, will be considered. These current DLT criteria will be applied retroactively for all patients treated with TSR-033 in combination with dostarlimab and for patients treated with TSR-033 monotherapy.

3.1.2. Rationale for the TSR-033 Starting Dose

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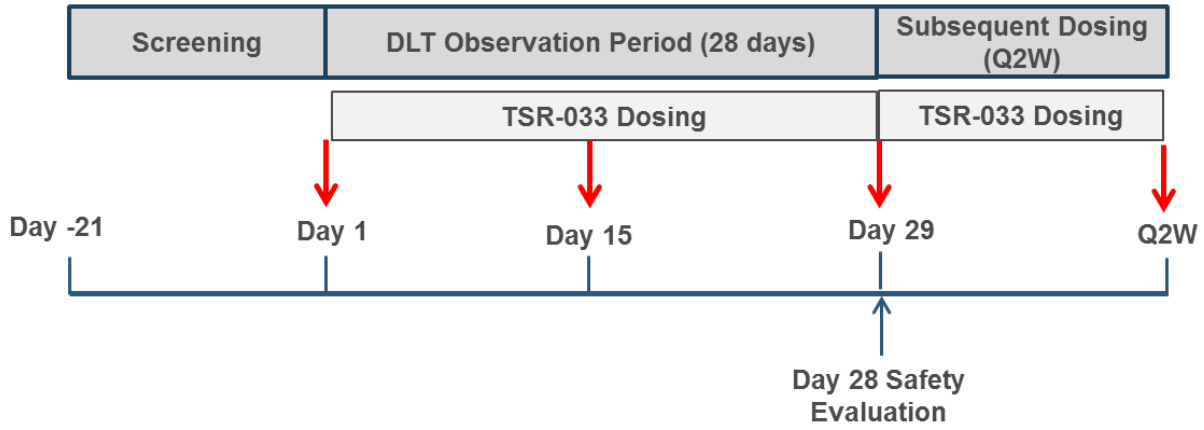
3.1.3. Part 1 – Dose Escalation

3.1.3.1. Part 1a: TSR-033 Monotherapy (Q2W)

Part 1a (monotherapy dose escalation) will evaluate TSR-033 at ascending doses (20 mg, 80 mg, and 240 mg). A higher dose level of 720 mg, or intermediate dose levels may be explored, if warranted based on target exposure and safety findings. TSR-033 will be administered via an approximately 30-minute IV infusion Q2W. The DLT observation period in Part 1a is defined as 28 days, encompassing 2 Q2W administrations of TSR-033.

Cohorts will be enrolled sequentially and will initially follow a 3+3 design at a starting dose of 20 mg, as determined by preclinical safety and pharmacology studies. Initially, 3 patients will be administered TSR-033, and dose escalation or expansion to 6 patients will be considered after all 3 patients at the 20-mg level have completed the DLT observation period and are found to be evaluable for safety upon review of safety data conducted by the Investigators and Sponsor. In subsequent dose levels, 6 patients will initially be enrolled into each cohort to evaluate ascending doses of TSR-033. At any dose level where DLTs are observed in ⅓ of patients, up to 6 additional patients may be enrolled in that dose level. The potential enrollment of additional patients will take place following discussion with the Investigators, taking into account severity and duration of observed DLTs as well as the overall safety of a dose level.

Figure 2: Part 1a Dosing Schema – TSR-033 Monotherapy (Q2W Schedule)



Abbreviations: DLT=dose limiting toxicity; Q2W=every 2 weeks.

At any dose level, an initial 3 or 6 patients will be enrolled, then:

- If the observed DLT rate is <⅓, the dose may be escalated.
- If the observed DLT rate is >⅓, no further dose escalation will be considered, and this dose level will be considered the maximum administered dose (MAD).
- If the observed DLT rate is ⅓, the Sponsor may enroll up to 6 additional patients following discussion with the Investigators.
  - If the observed DLT rate in a total cohort of 9 to 12 patients is ≥⅓, no further dose escalation will be considered, and this dose level will be considered the MAD.

The MTD will be considered the dose one level below the MAD if ≥⅓ of patients experience DLTs, or, at MAD if <⅓ of patients experience DLTs.

Accordingly, the RP2D may be at the MAD or 1 dose level below the MAD. Alternatively, an intermediate dose level below the MAD may be introduced and assessed for DLTs. Dose escalation will continue until the RP2D is reached or may be stopped at any dose level based on emerging safety and PK/PDy data, subject to agreement between the Investigators and Sponsor. A RP2D will be defined as the dose with DLTs observed in <⅓ of at least 6 patients and desired PK and CCI as determined by the Sponsor, in agreement with the Investigators. A patient will be considered non-evaluable if, for any reason other than safety, the patient is unable to complete the DLT observation period, or if the PK assessments were insufficient to define the PK profile. Patients in Part 1a considered non-evaluable may be replaced after consultation between the Investigators and Sponsor.

3.1.3.2. Part 1b: TSR-033 Monotherapy PK/PDy Cohort (Q2W Schedule)

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Figure 3: Part 1b Dosing Schema – PK/ 

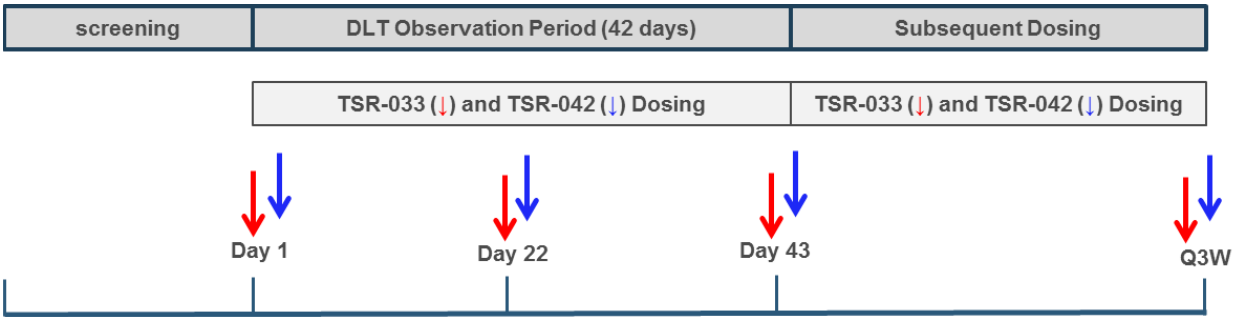
Abbreviations: PDy=pharmacodynamic; PK=pharmacokinetic; Q2W=every 2 weeks.

3.1.3.3. Part 1c: TSR-033 in Combination with Dostarlimab (Q3W Schedule)

The starting dose of TSR-033 when used in combination with dostarlimab must be 1 dose level below the highest dose at which <⅓ of at least 6 patients experienced DLTs with single agent TSR-033.

TSR-033 will be administered with dostarlimab Q3W throughout Part 1c, and patients will receive dostarlimab at a dose of 500 mg in combination with ascending doses of TSR-033 Q3W. The starting dose of TSR-033 when used in combination with dostarlimab must be one dose level below the highest dose at which <⅓ of patients experienced DLTs with single-agent TSR-033. Planned dose levels of TSR-033 include 80 and 240 mg. A higher dose level of 720 mg Q3W may be explored if warranted based on target exposure and safety findings. Additional cohorts consisting of 6-12 patients are needed to examine additional dose levels may also be explored if warranted following agreement between the Investigators and Sponsor. dostarlimab at a dose of 1000 mg may also be tested with the RP2D of TSR-033 given on a Q6W schedule. For all administrations of the combination regimen, TSR-033 will be given first, followed by dostarlimab.

Figure 4: Part 1c Dosing Schema – TSR-033 Combined with Dostarlimab (Q3W)



Abbreviations: DLT=dose-limiting toxicity; Q3W=every 3 weeks.

The RP2D will be defined by the Sponsor in agreement with Investigators based on safety, PK, and PDy data in a minimum of at least 6 patients. If DLT is observed in ≥⅓ patients, additional cohort(s) may be opened where a lower dose of either TSR-033 or dostarlimab, or both, may be explored.

3.1.3.3.1. Assessment of Renal Impairment

During the conduct of the expansion cohorts, a safety assessment will be performed in 6-12 patients with moderate chronic kidney damage (ie, creatinine clearance [CrCL] between 30 and 50 mL/min). Patients meeting these criteria may be enrolled in any of the 4 expansion cohorts and will complete DLT observation for 42 days. If DLTs are observed in <⅓ of patients, then patients with CrCL ≥30 mL/min will be allowed throughout Part 2 of the study.

3.1.4. Part 2 – Dose Expansion Cohorts – TSR-033 + Dostarlimab (Q2W + Q6W)

Part 2 will commence using the RP2D established for the combination regimen in Part 1c of the study. Study treatment in Part 2 will be administered on a Q2W schedule for TSR-033 and a Q6W schedule for dostarlimab. In Part 2B, TSR-033 and dostarlimab will be administered on Day 3 of a dose cycle following chemotherapy and bevacizumab therapy on Day 1 of a dose cycle.

The expansion cohorts will evaluate the preliminary activity of TSR-033 in combination with dostarlimab in anti-PD-1 naïve patients with a specific tumor type as follows:

- Cohort A – Third- and fourth-line MSS-CRC
- Cohort B –Second-line MSS-CRC

In each disease-specific expansion cohort, a Simon's 2-stage design will be used to provide initial assessment of the clinical activity of the TSR-033 in combination with dostarlimab[50] (see Section 8.7).

For Cohorts B1 and B2, if within 12 weeks of initiating study treatment, delayed irAEs consistent with DLT criteria occur in ≥⅓ of patients at a particular dose level, a lower dose level will be considered by the Sponsor following discussion with study Investigators for:

- Further refinement of RP2D and dose for expansion cohorts and/or
- All patients on treatment if in the best interest of the patient

3.2. Number of Subjects

Approximately 127-187 patients are expected to enroll in this study (allowing for replacement of patients and dose expansion).

Part 1: A total of up to 72-132 patients are anticipated:

Part 1a (TSR-033 monotherapy dose escalation): Approximately 30 to 54 patients

Part 1b (TSR-033 monotherapy PK/[redacted]*:* Approximately 18 to 30 patients

Part 1c (TSR-033 + dostarlimab combination dose escalation): Approximately 24 to 48 patients

These enrollment numbers could increase if the Sponsor, in consultation with the Investigator, determines that additional cohorts consisting of 6-12 patients are needed to examine additional dose levels.

Part 2: A total of up to approximately 55 patients are anticipated:

Cohort A (TSR-033 + dostarlimab in anti-PD-1-naïve third- and fourth-line CRC): Approximately 31 patients

CRC Cohort B1 (TSR-033 + dostarlimab given in combination with mFOLFOX6 and bevacizumab (SOC) in anti-PD-1-naïve second-line MSS-CRC patients who have progressed on frontline treatment with FOLFIRI, with or without biologics): Approximately 12 patients.

CRC Cohort B2 (TSR-033 + dostarlimab given in combination with FOLFIRI and bevacizumab (SOC) in anti-PD-1-naïve second-line MSS-CRC patients who have progressed on frontline treatment with FOLFOX [or variant], with or without biologics): Approximately 12 patients.

Should enrollment in Cohort B1 fall behind, allowance will be made to increase the number of patients enrolled in Cohort B2 after DLT clearance of the first 6 patients, such that an additional 6 to 18 may be enrolled. The total for Part 2B as a whole remains at 24.

3.3. General Study Conduct

Following the informed consent process, all patients will undergo screening procedures within 21 days (Part 1) or 28 days (Part 2) prior to the first dose of study treatment to determine eligibility for study entry. Screening procedures include assessment of patient history (medical, surgical, cancer, medication), complete physical examination (including vital signs, height, and weight), electrocardiogram (ECG), determination of patient Eastern Cooperative Oncology Group (ECOG) performance status (PS), and clinical laboratory tests (see Section 6.1.7).

3.3.1. Study Visits and Assessments

3.3.1.1. Biopsies

Biopsies are an integral component of this study to enable an assessment of the PDy effects of TSR-033 as a monotherapy and in combination with dostarlimab. Data from these investigations may contribute to the understanding of the tumor microenvironment, including, but not limited to, immune cells, tumor characteristics, and immune-related gene and protein expression and how they relate to TSR-033 clinical activity. Pre-dose and on-study/EOT biopsies are optional for patients in Parts 1a and 1c. For all patients in 1b and Part 2, fresh biopsies are required. For

patients in cohorts A and B, CCI [redacted] CCI [redacted] CCI [redacted] It is preferred that for tumor biopsies that are not simply incisional or excisional, a 16-gauge core biopsy needle is used; however, a smaller bore needle may be used if considered necessary for the patient's safety. Four core biopsies need to be obtained. Fine needle biopsies are not recommended for this study. Pleural effusions or lung aspirate samples cannot be substituted for tumor biopsies. Patients undergoing tumor biopsy must have prothrombin time (PT)/activated partial thromboplastin time (aPTT) <1.5 × upper limit of normal (ULN). Details regarding tumor tissue sample collection and management are provided in the Study Laboratory Manual and as follows:

- Archival tumor tissue is required at screening for all patients in Part 1a, 1b, and 1c. Archival tumor tissue may be submitted as formalin-fixed paraffin-embedded (FFPE) block (preferred) or slides. If archival tumor tissue is not available, patients must undergo a tumor tissue biopsy at screening (prior to dosing). For Part 2, submission of sufficient high-quality FFPE archival tissue is recommended, if available, to enable a longitudinal analysis of tumor biomarkers.
- Separate from archival tumor tissue, serial tumor tissue biopsies are OPTIONAL for Part 1a and 1c and REQUIRED for Part 1b and Part 2. Fresh serial tumor tissue biopsies are to be collected prior to treatment, approximately 4 to 6 weeks after treatment, and, whenever possible, at the time of PD and or EOT.

There may be instances where patients are enrolled and it is subsequently determined that, for medical reasons, a fresh tumor tissue biopsy cannot be obtained. The reason for the missed biopsy must be documented in the medical record. Refer to Section 6.6.2.

3.3.1.2. Safety Assessments

Safety assessments conducted throughout the treatment period include symptom-directed physical examinations, vital signs, ECGs, ECOG PS, 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 (ie, thyroid-stimulating hormone [TSH], triiodothyronine [T3], free triiodothyronine [FT3], thyroxine [T4], free thyroxine [FT4], or equivalent tests, where applicable), urinalysis, and pregnancy testing.

3.3.1.3. Radiographic Disease Assessments and Tumor Markers

Radiographic evaluations (computed tomography [CT]/magnetic resonance imaging [MRI] of chest, abdomen, and pelvis, or other regions known to have disease involvement) to assess extent of disease will be conducted Q6W (42 days ±7 days) for the first 3 assessments and every 9 weeks thereafter, or until radiographic confirmed PD or initiation of new systemic anti-cancer therapy, whichever occurs first. Additionally, patients will have appropriate testing of serum-

based tumor markers where applicable (eg, carcinoembryonic antigen [CEA] for patients with CRC) to coincide approximately with radiographic assessments. All on-study tumor assessments (radiographic and tumor markers) will be performed independent of dose 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 SOC. After 1 year, patients who remain on treatment will have imaging performed every 12 weeks (84 ±7 days). If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up (FUP), radiographic scans and appropriate testing of [redacted] should continue at the specified intervals. In Part 2, copies of scans will be collected and stored at a repository for potential evaluation.

Per RECIST v1.1, 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, whichever is clinically indicated.

Based on a recognized phenomenon of transient tumor flare in the first few months after the start of immunotherapy with subsequent disease response, patients treated with TSR-033 will be permitted to continue treatment beyond initial RECIST v1.1-defined PD while awaiting confirmation of PD.[51] In instances where pseudoprogession is suspected, PD should be confirmed a minimum of 4 weeks and up to 6 weeks after the first PD assessment in accordance with the [redacted] guidelines (see Section 6.3.1.5 and Appendix 2). Treatment may continue based on Investigator judgement if the patient is clinically stable (ie, no signs or symptoms of clinically significant or rapid progression of disease, including worsening of laboratory values or decline in PS; no progressive tumor at critical anatomical sites [eg, cord compression, intracranial tumor hemorrhage, etc.] requiring urgent medical intervention). Clinically stable patients should not be discontinued until progression is confirmed (see Appendix 2 for [redacted] detailed guidance).

3.3.1.4. Pharmacokinetics and Antidrug Antibody Assessments

Blood samples for the determination of serum levels of TSR-033 and dostarlimab, as well as antidrug antibodies (ADAs) formed against these investigational products, will be collected from patients in both Part 1 and Part 2.

In Part 1b, a cohort(s) of up to 6 additional patients may be enrolled in any dose level with DLTs observed in <⅓ of patients to better characterize the PK profile [redacted] following treatment with TSR-033. In this cohort(s), patients will receive their TSR-033 doses on Day 1, Day 29, and continue Q2W thereafter. The extended treatment durations in the absence of a Day 15 dose enables better characterization of the terminal phase of the PK profile, which can lead to more accurate calculations of PK parameters (such as $t_{½}$). Additionally, this extended treatment interval will provide additional [redacted] that may contribute to the determination of the RP2D. The decision regarding which cohort(s) to expand for this evaluation will be determined by the Sponsor and the Investigators.

The serum samples for PK determination will be analyzed using enzyme-linked immunosorbent assay (ELISA).

3.3.1.5. Pharmacodynamics Assessments

CCI

[redacted]

3.3.1.6. End of Treatment and Follow-Up Assessments

The EOT visit will occur within 7 days of the decision to discontinue study treatment for any reason. Should the first dose of a new anti-cancer therapy occur within 14 days of the decision to discontinue study treatment, all assessments required for the Safety FUP visit should occur at the EOT visit, and this visit will be considered the Safety FUP visit. If the first dose of the new anti-cancer therapy occurs >14 days after the decision to discontinue study, the Safety FUP visit will occur 30 ±7 days after the last dose of the study drug, or at the start of any new anti-cancer therapy, whichever occur first.

3.3.1.7. Adverse Events Follow-up

All AEs and SAEs will be collected and recorded for each patient from the day of signing the informed consent form (ICF) until 90 days after cessation of study treatment (or until alternative anti-cancer therapy is initiated, whichever occurs first), and any pregnancies are to be captured through 150 days post treatment. If an Investigator becomes aware of an SAE after the 90-day FUP period following treatment discontinuation 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 Section 6.1.5. All AEs and SAEs experienced by a patient during the study period, irrespective of the suspected causality, will be monitored until: the AE or SAE has resolved or stabilized, abnormal laboratory values have returned to baseline or normalized, there is a satisfactory explanation for the changes observed, the patient is lost to FUP, the patient withdraws consent, or the patient has died.

3.3.2. Study Treatment Duration

Patients in Part 1 and 2 may continue treatment with TSR-033 monotherapy or combination treatment for up to 2 years unless specific withdrawal criteria are met (Section 4.3). Continued treatment beyond 2 years may be considered following discussion between the Investigators and Sponsor.

3.3.3. End of Study and Final Analysis

The end of study is defined as the date when the last patient on study has completed his/her last study visit.

The final data cut-off (DCO) date for the study will be defined by the Sponsor and will be communicated to all sites. The DCO date represents the end of data collection for the study and the date on which the clinical study database will be closed to new data.

Patients in Survival Follow-Up at the time of the DCO date will be considered to have completed the study. Patients still on treatment at the time of the DCO date may continue to receive study treatment for up to 2 years unless specific withdrawal criteria are met (see Section 3.3.2 and Section 4.3.1); patients may also choose to discontinue study treatment at any time. *Note:* Study treatment must be discontinued before the TSR-033 study drug supply expires.

Patients who continue study treatment will be monitored and receive follow-up care in accordance with standard local clinical practice. Assessments will revert to the standard of care at a patient's particular study site, and only SAEs, AEs leading to discontinuation of study treatment, overdoses, and pregnancies will be reported directly to the Sponsor via paper forms (see Section 6.1.12; refer to the Study Reference Manual for further details on reporting using paper forms). Although the clinical study database will be closed at the time of the DCO date, the study will remain open until all patients discontinue study treatment and the end of study definition (noted above) is reached.

4. STUDY POPULATION

4.1. Inclusion Criteria

4.1.1. Inclusion Criteria for Patients in Part 1

1. The patient is ≥18 years of age.
2. The patient has any histologically or cytologically confirmed advanced (unresectable) or metastatic solid tumor and has PD after treatment with available therapies that are known to confer clinical benefit or who are intolerant to treatment.
3. The patient must have an archival tumor tissue sample that is FFPE (blocks preferred over slides) and requested and confirmed available from offsite locations prior to dosing. The quality and quantity of the sample must be confirmed sufficient as per the Study Laboratory Manual. Patients who do not have archival tissue must agree to a fresh tumor tissue biopsy prior to dosing.
4. Part 1b (PK/PDy cohort): The patient must have lesions amenable for biopsy and agree to undergo biopsies for fresh tumor tissue prior to treatment, approximately 4 to 6 weeks after treatment, and, whenever possible, at the time of PD and/or EOT. Serial biopsies are optional for patients in Part 1a and 1c.
5. Female patients must have a negative serum or urine pregnancy test within 72 hours prior to the date of the first dose of study medication if of childbearing potential or be of non-childbearing potential. Non-childbearing potential is defined as:
    a. ≥45 years of age and has not had menses for >1 year.
    b. Amenorrhoeic for <2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon pre-study (screening) evaluation.
    c. Post hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must fulfill the criteria in Inclusion Criterion 5.
6. Female patients of childbearing potential (ie, those who do not meet a-c above) must agree to use 2 highly effective forms 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.
7. The patient must have an ECOG PS of ≤1.
8. The patient has adequate hematologic and organ function, defined as:
    a. ANC ≥1,500/µL.
    b. Platelets ≥100,000/µL.
    c. Hemoglobin (Hb) ≥9 g/dL or ≥5.6 mmol/L.

- *Note:* Patients with Hb 7 to ≤9 g/dL (without bleeding) may be transfused prior to dosing in order to meet eligibility criteria; however, Hb should remain stable and ≥9 g/dL for at least 1 week.

d. Serum creatinine ≤1.5 × ULN or calculated CrCL ≥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 (in the event that the total bilirubin result exceeds the upper institutional limits of normal, direct bilirubin will be obtained to determine eligibility).
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) of PT ≤1.5 × ULN, unless patient is receiving anticoagulant therapy, then PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants; aPTT) ≤1.5 × ULN unless patient is receiving anticoagulant therapy, then PT or PTT is within therapeutic range of intended use of anticoagulants.

4.1.2. Inclusion Criteria for Patients in Part 2

1. The patient is ≥18 years of age.
2. The patient has any histologically or cytologically confirmed CRC that is metastatic or not amenable to potentially curative resection (advanced), in the opinion of the Investigator.
3. The patient has a primary and/or metastatic tumor(s) that is known to be MSS, as determined locally.
4. The patient must have lesions amenable for biopsy and agree to undergo biopsies for fresh tumor tissue prior to treatment, approximately 4 to 6 weeks after treatment, and, whenever possible, at EOT and/or the time of PD. If the patient has had a biopsy prior to entering the 28-day screening period, and within approximately 12 weeks of study treatment, that biopsy sample may be accepted as the baseline fresh biopsy. Additionally, submission of sufficient high-quality archival tumor tissue is recommended, if available, to enable a longitudinal analysis of tumor biomarkers.
5. The patient has measurable disease by RECIST v.1.1.
6. The patient has resolution to Grade ≤1, per CTCAE v5.0, of all clinically significant toxic effects of prior chemotherapy, surgery, radiotherapy, or hormonal therapy, with the exception of peripheral neuropathy, which must have resolved to Grade ≤2, and except where otherwise noted in the eligibility criteria.
7. Female patients must have a negative serum or urine pregnancy test within 72 hours prior to the date of the first dose of study medication if of childbearing potential or be of non-childbearing potential. Non-childbearing potential is defined as:

   a. ≥45 years of age and has not had menses for >1 year.
   b. Amenorrhoeic for <2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon pre-study (screening) evaluation.

c. Post hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must fulfill the criteria in Inclusion Criterion 5.

8. Female patients of childbearing potential (ie, those who do not meet a-c above) must agree to use 2 highly effective forms 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.
9. The patient has an ECOG PS of ≤1.
10. The patient has adequate hematologic and organ function as defined:
    a. ANC ≥1,500/µL
    b. Platelets ≥100,000/µL.
    c. Hb ≥9 g/dL or ≥5.6 mmol/L.
        – *Note:* Patients with Hb 7 to ≤9 g/dL (without bleeding) may be transfused prior to dosing in order to meet eligibility criteria; however, Hb should remain stable and ≥9 g/dL for at least 1 week.
    d. Serum creatinine ≤1.5 × ULN or calculated CrCL ≥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 (in the event that the total bilirubin result exceeds the upper institutional limits of normal, direct bilirubin will be obtained to determine eligibility).
    f. AST and ALT ≤2.5 × ULN unless liver metastases are present, in which case they must be ≤5 × ULN
    g. INR of PT ≤1.5 × ULN, unless patient is receiving anticoagulant therapy, then PT or PTT is within therapeutic range of intended use of anticoagulants; aPTT) ≤1.5 × ULN unless patient is receiving anticoagulant therapy, then PT or PTT is within therapeutic range of intended use of anticoagulants.
    h. Urinary protein is ≤1+ on dipstick for routine urinalysis; if urine protein ≥2+, a 24-hour urine sample must be collected and must demonstrate <1000 mg of protein in 24 hours to allow participation in the study.
    i. Baseline albumin ≥3.0 g/dL.

4.1.2.1. Inclusion Criteria for Patients in Part 2A

1. The patient must have had at least 2, but no more than 3, prior lines of therapy in the advanced or metastatic setting. Adjuvant chemotherapy with radiographic progression >12 months after the last dose will not be considered a line of therapy.
2. The patient has progressed on standard therapies or withdrawn from standard treatment due to unacceptable toxicity. Previous standard treatment must include all of the following:
    a. Fluoropyrimidine.

b. Oxaliplatin: Patients treated with oxaliplatin in adjuvant setting should have progressed after 12 months of completion of adjuvant therapy or they must have been treated with oxaliplatin for metastatic disease.
c. Irinotecan.
d. Patients whose disease is known to be RAS-wild-type must have been treated with cetuximab, panitumumab, or other EGFR inhibitor for metastatic disease.
e. Bevacizumab and/or another anti-angiogenic agent.
f. Previous treatment with regorafenib and/or TAS-102 are allowed in the absence of contraindications and if these agents are available to the patient according to local standards.

3. Time between the patient's last chemotherapy and enrollment must be ≤8 weeks.

4.1.2.2. Inclusion Criteria for Patients in Part 2B

4. The patient has received ≤2 prior systemic chemotherapy regimens in any setting (only 1 prior regimen for metastatic disease is permitted).

4.1.2.2.1. Inclusion Criteria for Patients in Part 2 Cohort B1

1. The patient has received first-line combination therapy consisting of bevacizumab or anti-EGFR antibodies with FOLFIRI and has experienced radiographic progression during or after first-line therapy. Radiographic progression >12 months after the last dose of adjuvant therapy will not be considered a line of therapy.
2. mFOLFOX6 therapy with bevacizumab is appropriate for the patient and is recommended by the Investigator.

4.1.2.2.2. Inclusion Criteria for Patients in Part 2 Cohort B2

1. The patient has received first-line combination therapy consisting of bevacizumab or anti-EGFR antibodies with FOLFOX (or a variant) and has experienced radiographic progression during first-line therapy. Radiographic progression >12 months after the last dose of adjuvant therapy will not be considered a line of therapy.
2. FOLFIRI therapy with bevacizumab is appropriate for the patient and is recommended by the Investigator.

4.2. Exclusion Criteria

4.2.1. General Exclusion Criteria for All Patients

1. The patient has previously been treated with an anti-LAG-3 antibody.
2. The patient has known uncontrolled central nervous system (CNS) metastases and/or carcinomatous meningitis.
3. The patient has a known concurrent, serious, uncontrolled medical disorder, nonmalignant systemic disease, or active infection requiring systemic therapy, including human immunodeficiency virus (HIV), known active hepatitis B or hepatitis C, active infection, or active autoimmune disease.

4. The patient is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study.
5. The patient has a history of interstitial lung disease.
6. The patient has not recovered (ie, to Grade ≤1 or to baseline) from radiation- and chemotherapy-induced AEs, has received transfusion of blood products (including platelets or red blood cells), or has received administration of colony stimulating factors (including granulocyte colony-stimulating factor [G-CSF], granulocyte macrophage colony-stimulating factor or recombinant erythropoietin) within 3 weeks prior to the first dose of study drug.
7. The patient is currently participating in an investigational study (therapy or device) or has participated in an investigational study within 4 weeks prior to the first dose of study drug.
8. The 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 the first dose of study drug, whichever is shorter.
9. The patient has received wide-field (full-dose pelvic) radiotherapy within 28 days prior to the first dose of study drug.
10. The patient has a history of uncontrolled hereditary or acquired bleeding or thrombotic disorders.
11. The patient has experienced any arterial thrombotic or arterial thromboembolic events, including, but not limited to myocardial infarction, transient ischemic attack, or cerebrovascular accident, within 12 months prior to first dose of study drug.
12. The patient has received a prior autologous or allogeneic organ or transplantation.
13. The patient has undergone major surgery within 28 days or subcutaneous venous access device placement within 7 days prior to the first dose of study drug.
14. The patient has had a serious nonhealing wound, ulcer, or bone fracture within 28 days prior to first dose of study drug.
15. The patient has an elective or planned major surgery to be performed during the course of the trial.
16. The patient has a history of inflammatory bowel disease or Crohn's disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery) in the 12 months prior to the first dose of study drug.
17. The patient has an acute or subacute bowel obstruction, abdominal fistula, or history of chronic diarrhea which is considered clinically significant, in the opinion of the Investigator.
18. The patient has experienced a Grade ≥3 bleeding event within 3 months prior to the first dose of study drug.
19. The patient has either peptic ulcer disease associated with a bleeding event or known active diverticulitis.

20. The patient has not recovered (Grade ≥1) from AEs and/or complications from any major surgery prior to the first dose of study drug.
21. The patient has received a vaccine within 7 days of the first dose of study drug.
22. The patient has known hypersensitivity to TSR-033, dostarlimab (Part 1c and Part 2), or associated excipients.

4.2.1.1. Exclusion Criteria for Patients in Part 1

1. The patient's prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-LAG-3 agent resulted in permanent discontinuation due to an AE.

4.2.1.2. Exclusion Criteria for Patients in Part 2

1. The patient has been previously treated with an anti-PD-1 or anti-PD-L1 antibody.

4.2.1.3. Exclusion Criteria for Patients in Part 2B

1. The patient has known dihydropyrimidine dehydrogenase deficiency.
2. The patient experienced an arterial thrombotic/thromboembolic event, Grade 4 hypertension, Grade 4 proteinuria, a Grade 3-4 bleeding event, or bowel perforation during first-line therapy with a bevacizumab-containing regimen.
3. The patient has known hypersensitivity to bevacizumab, mFOLFOLX6 (Cohort B1) or FOLFIRI (Cohort B2), or associated excipients.
4. The patient experienced PD within 12 months of last dose of adjuvant therapy.

4.3. Patient Withdrawal and Replacement

4.3.1. Discontinuation from Study Treatment

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

- AE, which may include DLTs, irAEs per guidance in Table 3, and non-resolving AEs where continued treatment could be detrimental to patient's well-being.
- Disease progression as outlined in Section 6.3 or based on clinical criteria by Investigator.
- Risk to patients as judged by the Investigator, Sponsor, or both.
- Severe noncompliance with protocol as judged by the Investigator, Sponsor, or both
- 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.

- Withdrawal of consent from treatment, but agreement to participate in FUP visits (partial consent withdrawn).
- Death.

Patients who discontinue from study treatment will continue to receive FUP assessments (see Table 4, Table 5, Table 6, and Table 7) as part of the study unless they are discontinued from the study.

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 FUP.
- Death.
- Sponsor decision to terminate study.

If a patient is thought to be lost to FUP, 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 FUP, at least 3 documented attempts, including 1 via certified mail, should be made to contact the patient before the patient is deemed lost to FUP.

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 or if there is insufficient PK data during Part 1a, Part 1b, and Part 1c.

For Cohorts B1 and B2, if a patient discontinues study treatment prior to the first assessment of disease (either scheduled radiological assessment at 6- or 9-weeks post treatment initiation or clinically indicated disease assessment prior to 6 or 9 weeks), the patient may be replaced after consultation between the Investigators and Sponsor, unless the patient discontinued study treatment due to clear clinical progression without radiographic evidence of progression. In these patients, obtaining a subsequent confirmatory radiographic image is necessary if feasible (eg, patient's condition allows for imaging).

4.4. Patient Identification and Randomization

4.4.1. Patient Identification

All patients who enter screening (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 consented, been screened, and all eligibility criteria have been confirmed by the Investigator. The patient identification number must remain constant throughout the entire study.

4.4.2. Randomization Scheme

Not applicable.

5. STUDY MEDICATION

5.1. Identity

5.1.1. Investigational Products

TSR-033 is a humanized monoclonal IgG4 antibody and will be supplied as a solution in vials containing 80 and 160 mg (4 mL and 8 mL fill volumes at 20 mg/mL, respectively).

Dostarlimab (previously referred to as TSR-042) is an IgG4 antibody and will be supplied as a solution in vials containing 500 mg (50 mg/mL).

5.1.2. Non-Investigational Products

In Part 2B the investigational products TSR-033 and dostarlimab will be administered in combination with the current SOC treatment for CRC, which is chemotherapy (mFOLFOX6 or FOLFIRI) with bevacizumab.

mFOLFOX6 and FOLFIRI are combinations of folinic acid (FOL)/leucovorin, 5-fluorouracil (F), and either oxaliplatin (OX) or irinotecan (IRI), respectively, which act as systemic cytotoxic agents.

Bevacizumab is a humanized monoclonal IgG1 antibody that targets VEGF-A to inhibit angiogenesis.

Both the chemotherapeutic agents and the biologic, bevacizumab, administered in this study, are not investigational products and will be obtained from local sources as commercially available dosage formulation. *Note:* Biosimilars of bevacizumab are permitted for administration as a substitute for bevacizumab. Administration of a biosimilar of bevacizumab must be recorded in the electronic case report form (eCRF) as a concomitant medication (Section 5.6.1).

5.2. Administration

TSR-033 will be administered using an approximately 30-minute IV infusion on Day 1. Start and stop times for infusion will be recorded in the eCRF.

Part 1a: TSR-033 will be administered every 14 days ±1 day (Q2W). The planned ascending doses in Part 1a of the study are 20, 80, and 240 mg Q2W. Further dose escalation to 720 mg Q2W may also be assessed in an additional cohort(s) following agreement between the Investigators and Sponsor. Additional cohorts consisting of 6-12 patients to examine additional dose levels may also be explored, if warranted, following agreement between the Investigators and Sponsor.

Part 1b: A cohort(s) of up to 6 additional patients may be enrolled in any dose level with DLTs observed in <⅓ of patients to better characterize the PK profile of TSR-033 CCI [redacted] CCI [redacted] In this cohort(s) patients will receive their TSR-033 dose on Day 1, Day 29 and continue Q2W thereafter.

Part 1c: TSR-033 will be administered with dostarlimab Q3W throughout Part 1c, and patients will receive dostarlimab at a dose of 500 mg in combination with ascending doses of TSR-033 Q3W. The starting dose of TSR-033 when used in combination with dostarlimab must be one

dose level below the highest dose at which <⅓ of patients experienced DLTs with single-agent TSR-033. Planned dose levels of TSR-033 include 80 and 240 mg. A higher dose level of 720 mg Q3W may be explored, if warranted, based on target exposure and safety findings. Additional cohorts consisting of 6-12 patients to examine additional dose levels may also be explored, if warranted, following agreement between the Investigators and Sponsor. dostarlimab at a dose of 1000 mg may also be tested with the RP2D of TSR-033 given on a Q6W schedule. For all administrations of the combination regimen, TSR-033 will be given first, followed by dostarlimab.

Part 2A: Following completion of the TSR-033 infusion, dostarlimab (1000 mg) will be administered via a 30-minute IV infusion (-5 minute and +15 minute) with a post-infusion observation period of 2 hours for Dose 1, Day 1. TSR-033 will be given on a Q2W schedule and dostarlimab on a Q6W schedule. If emerging safety and/or PK data indicate that exploration of a lower TSR-033 dose is warranted, an additional cohort may be opened.

Part 2 Cohort B1: Initially, a 6-patient run-in with mFOLFOX6 plus bevacizumab regimen will be tested for safety, with the potential to add 6 additional patients, for a total of 12 patients. The DLT observation period will be from Dose 1, Day 1, through Dose 3, Day 3, prior to the start of infusion. Following the DLT observation period, if ≥2 DLTs are observed, a dose level reduction of TSR-033 to 240 mg can be considered (dose level -1). This dose level would then enroll 6 patients. Alternatively, if <2 DLTs are observed during the DLT observation period, 6 additional patients may be enrolled at that dose level to confirm safety and collect preliminary efficacy data.

Part 2, Cohort B2: Initially, a 6-patient run-in with FOLFIRI plus bevacizumab regimen will be tested for safety, with the potential to add 6 additional patients, for a total of 12 patients. The DLT observation period will be from Dose 1, Day 1, through Dose 3, Day 3, prior to the start of infusion. Following the DLT observation period, if ≥2 DLTs are observed, a dose level reduction of TSR-033 to 240 mg can be considered (dose level -1). This dose level would then enroll 6 patients. Alternatively, if <2 DLTs are observed during the DLT observation period, 6 additional patients may be enrolled at that dose level to confirm safety and collect preliminary efficacy data.

Should enrollment in Cohort B1 fall behind, allowance will be made to increase the number of patients enrolled in Cohort B2 after DLT clearance of the first 6 patients, such that an additional 6 to 18 may be enrolled. The total for Part 2B as a whole remains at 24.

Please refer to the Pharmacy Manual for details on the preparation and administration of the infusion solutions for TSR-033 and dostarlimab.

The bevacizumab and the chemotherapy regimens will be administered following TSR-033 and dostarlimab administration. mFOLFOX6 or FOLFIRI and TSR-033 will be given on a Q2W schedule and dostarlimab on a Q6W schedule.

The full infusion schedule will be as follows:

Part 2 Cohort B1: Infusion times (per dose cycle):

Note: Infusion times described below are approximate.

1. Bevacizumab (Day 1): 30-minute infusion, unless a longer schedule was previously tolerated; 15 minutes observation (assuming previously tolerated).
2. Oxaliplatin with leucovorin (Day 1): 2-hour infusion. (Part of mFOLFOX6 regimen).
3. 5-Fluorouracil (Day 1): 2-4 minutes. (Part of mFOLFOX6 regimen).
4. 5-Fluorouracil (Day 1-3): continuous infusion, 46-hours. (Part of mFOLFOX6 regimen).
5. TSR-033 (Day 3): 30-minute infusion.
6. Dostarlimab (Day 3, every third dose of TSR-033): 30-minute infusion; 2 -hour observation for first dose. Should no infusion reactions (IRs) occur, observation can be reduced to 1 hour for second dose, then to 30 minutes thereafter.

Part 2 Cohort B2: Infusion times (per dose cycle):

Note: Infusion times described below are approximate.

1. Bevacizumab (Day 1): 30-minute infusion, unless a longer schedule was previously tolerated; 15 minutes observation (assuming previously tolerated).
2. Irinotecan with leucovorin (Day 1): 90 minutes. (Part of FOLFIRI regimen).
3. 5-Fluorouracil (Day 1): 2-4 minutes. (Part of FOLFIRI regimen).
4. 5-Fluorouracil (Day 1-3): continuous infusion, 46-hours. (Part of FOLFIRI regimen).
5. TSR-033 (Day 3): 30-minute infusion.
6. Dostarlimab (Day 3, every third dose of TSR-033): 30-minute infusion; 2-hour observation for first dose. Should no IRs occur, observation can be reduced to 1 hour for second dose, then to 30 minutes thereafter.

Part 2B Dosing Schema:

Wk 1	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11[a]**
Dose 1[b]		**Dose 2[b]**		**Dose 3[b]**		**Dose 4[b]**		**Dose 5[b]**		**Dose 6[b]**
Bevacizumab		**Bevacizumab**		**Bevacizumab**		**Bevacizumab**		**Bevacizumab**		**Bevacizumab**
mFOLFOX6[c] or FOLFIRI[d]		**mFOLFOX6[c] or FOLFIRI[d]**		**mFOLFOX6[c] or FOLFIRI[d]**		**mFOLFOX6[c] or FOLFIRI[d]**		**mFOLFOX6[c] or FOLFIRI[d]**		**mFOLFOX6[c] or FOLFIRI[d]**
TSR-033 (Day 3)		**TSR-033 (Day 3)**		**TSR-033 (Day 3)**		**TSR-033 (Day 3)**		**TSR-033 (Day 3)**		**TSR-033 (Day 3)**
Dostarlimab (Day 3)						**Dostarlimab (Day 3)**				

Abbreviation: Wk=week.

[a] This treatment regimen may be continued for so long as the patient is, in the opinion of the Investigator, benefiting from treatment.

[b] Drug administered on Day 1 unless otherwise noted.

[c] Cohort B1.

[d] Cohort B2.

5.2.1. Post-Treatment Vital Signs Monitoring and Safety Observation

For all patients in Part 1, vital signs (ie, resting blood pressure [BP], pulse, respiratory rate, and temperature) will be monitored around the administration of the first and second doses of TSR-033. These measurements should be collected prior to TSR-033 administration, 15 minutes after the start of the TSR-033 infusion (±5 mins), at the end of the TSR-033 infusion (±5 mins), 60 minutes (±15 minutes) after the end of the TSR-033 infusion, and 150 minutes (±15 minutes) after the end of the TSR-033 infusion. Vital signs on subsequent treatment days will be assessed and documented prior to the TSR-033 infusion and at the end of the TSR-033 infusion. Vital signs should be collected prior to blood draws.

For patients in Part 1 of the study, safety observation will take place for 4 hours post-TSR-033 or -TSR-033/dostarlimab administration, for Dose 1 and Dose 2 of TSR-033. For patients in Part 2, a 2-hour observation period will take place post-treatment administration for Dose 1; should no IRs occur, observation can be reduced to 1 hour for Dose 2, then to 30 minutes for all doses thereafter. Note that the observation period for patients receiving combination therapy (Part 1c and 2) will begin once the dostarlimab administration is completed. Also note that for patients in Part 2B, observation will be on Day 3 of the dose cycle when TSR-033/dostarlimab are administered post-Day 1/2 treatment with SOC chemotherapy and bevacizumab.

5.2.2. Dose of TSR-033

5.2.2.1. TSR-033 Dose (Part 1a and Part 1b) – Q2W Schedule

Part 1a (dose escalation) will initially evaluate 3 ascending dose levels of TSR-033, 20 mg, 80 mg, and 240 mg, administered via IV infusion. A 3 + 3 design will be used for the initial dose escalation (see Section 3.1.3.1 for details on dose escalation rules). Subsequent dose escalations will enroll 6-12 patients at each dose level. Further dose escalation may be considered in additional cohort(s) to 720 mg or an intermediate dose following agreement between the Investigators and Sponsor.

Once the DLT observation period for the 20 mg dose level in Part 1a is complete, a cohort of up to 6 patients at a dose of 20 mg will be enrolled in Part 1b. Additional cohorts may be enrolled in Part 1b at 80 or 240 mg, or both, or an alternative dose level, such as 720 mg, to better understand the PK/PDy of TSR-033.

5.2.2.2. TSR-033 in Combination with Dostarlimab (Part 1c) – Q3W Schedule

The starting dose of TSR-033 when used in combination with dostarlimab must be one dose level below the highest dose at which <⅓ of at least 6 patients experienced DLTs globally with single agent TSR-033. A lower dose cohort (6-12 patients) may be evaluated if emerging data indicate that further dose exploration is warranted. In Part 1c TSR-033 will be administered in combination dostarlimab at a flat dose of 500 mg. On a day of treatment, TSR-033 will be administered first, followed by dostarlimab.

5.2.2.3. TSR-033 in Combination with Dostarlimab (Part 2)

Part 2 of the study will further explore the safety and clinical activity of TSR-033 in combination with dostarlimab. In Part 2B, the TSR-033 + dostarlimab combination will be administered with

bevacizumab and chemotherapy (Cohort B1: mFOLFOX or Cohort B2: FOLFIRI). In Part 2, the following 2 disease specific cohorts will be enrolled (all patients PD-1 naïve):

- Cohort A: Third- or fourth-line CRC
- Cohort B: Second-line CRC

Dosing in Part 2 will be initiated using the RP2D established for TSR-033 in Part 1c of the study. Based on the analysis of TSR-033 exposure, receptor occupancy data, and PK/PDy modeling from Part 1, 720 mg Q2W is predicted to result in drug exposure sufficient to maintain adequate target engagement over the dosing interval in the majority of patients. The selection of the RP2D and schedule may subsequently be revised based on clinical and PK/PDy data initially obtained in Part 2.

TSR-033 should not be administered before the visit-required assessments are completed and laboratory test results and assessments are reviewed by the Investigator or sub Investigator.

5.3. Dose Modification

5.3.1. Dose Modification General Rules

- Intra-patient dose escalation to a TSR-033 dose that has been previously shown to be safe may be permitted following agreement between the Investigator and Sponsor.
- Study treatment dosing delays are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 28 days of the scheduled TSR-033 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.
- TSR-033 and dostarlimab must be withheld for drug-related Grade 3 toxicities but may be resumed upon recovery to Grade ≤1 (see Table 2 for certain exceptions); TSR-033 and dostarlimab will be permanently discontinued for any drug-related Grade 4 event. TSR-033 should be discontinued for some Grade 3 immunologic-mediated AEs as described in Table 2.
- Specific AEs typically observed with anti-PD-1 antibodies will be managed according to the rules summarized below in Section 5.3.2.
- In Part 2B, dose modification for bevacizumab, mFOLFOX6 (Cohort B1), or FOLFIRI (Cohort B2) should follow the product label. If, in the opinion of the Investigator, a patient may benefit from discontinuation of certain but not all elements of a regimen, for example, discontinue oxaliplatin but remain on the remainder of mFOLFOX6 plus bevacizumab and the immunotherapies, this will be allowed only after discussion with the Medical Monitor.

5.3.2. Dose Modification for Specific Immune-Related Adverse Events

- Any grade hypophysitis or hypothyroidism should be managed by endocrine replacement therapy. In case of new onset type 1 diabetes mellitus (T1DM)/Grade 3

or 4 hyperglycemia, holding the dose is required, but TSR-033 and dostarlimab may be resumed in appropriately managed clinically and metabolically stable patients. Please refer to Table 3 for details on the management of TSR-033 dose delays and discontinuation for specific events.

- For TSR-033, dose reductions to a lower dose level (no reduction below 20 mg) may be permitted following consultation with the Sponsor based on emerging data.
- All treatment delays (including any missed doses) and discontinuations, and the reason for delays or discontinuation of TSR-033 and/or dostarlimab, should be recorded in the eCRF.

Table 2: Dose Modifications for Non-Hematologic Toxicities – Applies to Both Study Drug Components (TSR-033 and Dostarlimab)

Toxicity	Hold Treatment for Grade	Restarting Treatment/Discontinuation
Diarrhea/colitis	2-3	Restart dosing when toxicity resolves to Grade 1.
	4 or recurrent 3	Permanently discontinue.
AST, ALT, or increased bilirubin	2 with AST or ALT >3 to ≤5 × ULN or total bilirubin >1.5 to ≤3 × ULN	Restart dosing when toxicity resolves to Grade 1.
	≥3 with AST or ALT >5 × ULN or total bilirubin >3 × ULN	Permanently discontinue (exception below[a]).
T1DM 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.
Severe neurological events (myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, immune-related encephalitis, transverse myelitis)	Any grade	Permanently discontinue.
Hypophysitis	2-4	For Grade 2-3 hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 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.
Hyperthyroidism	3	Hold until return to adequate hormone levels based on laboratory values and restart dosing when toxicity resolves to Grade 1.
	4	Permanently discontinue.

Table 2: Dose Modifications for Non-Hematologic Toxicities – Applies to Both Study Drug Components (TSR-033 and Dostarlimab) (Continued)

Toxicity	Hold Treatment for Grade	Restarting Treatment/Discontinuation
Infusion-related reaction	2[b]	Restart dosing when toxicity resolves to Grade 1.
	3-4	Permanently discontinue.
Pneumonitis	2	Restart dosing when toxicity resolves to Grade 1. If Grade 2 recurs, permanently discontinue.
	3-4	Permanently discontinue.
Severe exfoliative dermatologic events	Suspected DRESS, SJS, or TEN	Withhold.
	Confirmed DRESS, SJS, or TEN	Permanently discontinue.
Renal failure or nephritis	2 with creatine >1.5 to ≤3 × ULN	Restart dosing when toxicity resolves to Grade 1.
	≥3 with creatine >3 × ULN	Permanently discontinue.
Adrenal insufficiency	2-3	Hold until administration of hormone replacement therapy results in return to adequate hormone levels based on laboratory values and restart dosing when toxicity resolves to Grade 1. For recurrent or worsening Grade ≥2 adrenal insufficiency while adequate hormone replacement therapy is continuing, permanently discontinue.
	4	Permanently discontinue.
Hemophagocytic lymphohistiocytosis	Any grade	Permanently discontinue.
Myocarditis	2-4	Permanently discontinue.
Uveitis	≥2	Withhold.
Other irARs	Based on severity and type of reaction (2-3)	Withhold. Restart dosing when toxicity resolves to Grade 1.
	4 or recurrent 3	Permanently discontinue.
Recurrence of AEs after resolution to Grade 1	3-4	Permanently discontinue.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; DRESS=drug reaction with eosinophilia and systemic symptoms; irAR=immune-related adverse reaction; SJS=Stevens-Johnson syndrome; T1DM=type 1 diabetes mellitus; TEN=toxic epidermal necrolysis; 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 (eg, from 100 mL/h to 50 mL/h). 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 3).

5.4. Packaging, Labeling and Storage

TSR-033 for injection is supplied in vials containing 80 and 160 mg at a concentration of 20 mg/mL.

Dostarlimab for injection is supplied in vials containing 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 nonpatient-specific.

All study treatment supplies must be stored in accordance with the Pharmacy 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 Pharmacy Manual.

All dispensing 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 Pharmacy 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.

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 anti-cancer or biological therapy not specified in this protocol.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than TSR-033 and dostarlimab.

- Radiation therapy is prohibited within 3 weeks prior to study Day 1 and during study treatment.
  - Palliative radiation therapy to a small field >1 week prior to Day 1 of study treatment may be allowed after consultation with the Sponsor. During study treatment, radiation therapy is permitted to pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics, as long as no evidence of PD is present. The patient must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy may be considered clinical progression for the purposes of determining CCI
- Systemic glucocorticoids for any purpose other than to modulate symptoms of suspected immunologic etiology are not permitted.
  - The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. The use of corticosteroids is also permitted for patients with allergy to IV contrast for CT imaging scans. Inhaled corticosteroids (for the management of asthma), topical or locally injected steroids, and corticosteroid eye drops are permitted.
- Vaccines within 7 days prior to the first dose of study treatment are not permitted.
  - If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy may be required. The Investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the Investigator or the patient's primary physician, or both. The decision to continue the patient on study therapy, however, requires the mutual agreement of the Investigator, the Sponsor, and the patient.

5.6.3. Contraception

It is not known if TSR-033 or 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.[52] Therefore, nonpregnant, non-breastfeeding women may only be enrolled if they are willing to use 2 highly effective forms of contraception (from the list below) or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as: surgically sterilized, postmenopausal (a woman who is ≥45 years of age and has not had menses for >1 year will be considered postmenopausal), or not heterosexually active for the duration of the study.

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

Female patients should be informed that taking the study drug 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 Mediations 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 (eg, G-CSF) should be administered according to current American Society of Clinical Oncology guidelines.[51]

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

The following text details specific treatment guidance by type of AE:

- Pneumonitis:
  - Treat with systemic corticosteroids, oral for Grade 2 (eg, 0.5 to 1 mg/kg per day of prednisone or equivalent) and IV for Grade 3-4 (eg, 1 to 2 mg/kg per day of prednisone or equivalent).
  - Administer additional anti-inflammatory measures, as needed.
  - Taper corticosteroids when symptoms improve to Grade ≤1 over ≥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, and 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 (eg, 0.5 to 1.0 mg/kg per 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 (eg, 1 to 2 mg/kg per day of prednisone or equivalent) followed by high-dose oral steroids.
  - Taper corticosteroids when symptoms improve to Grade ≤1 over ≥4 weeks.

- T1DM 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 (eg, 0.5 to 1 mg/kg per day of prednisone or equivalent) and IV for Grade 3-4 (eg, 1 to 2 mg/kg per day of prednisone or equivalent).
  - Taper corticosteroids when symptoms improve to Grade ≤1 over ≥4 weeks.
  - Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Hyperthyroidism or Hypothyroidism:
  - Thyroid disorders have been reported with 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 nonselective beta-blockers (eg, propranolol) as initial therapy.
  - Grade 3-4 Hyperthyroidism
    - Treat with an initial dose of IV corticosteroids followed by oral corticosteroids (eg, 0.5 to 1 mg/kg per day of prednisone or equivalent). Taper corticosteroids when symptoms improve to Grade ≤1 over ≥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 SOC.
- Hepatitis:
  - Treat with systemic corticosteroids, oral for Grade 2 (initial dose of 1 to 2 mg/kg per day of prednisone or equivalent) and IV for Grade 3-4 (1 to 2 mg/kg per day of prednisone or equivalent)
  - Taper corticosteroids when symptoms improve to Grade ≤1 over ≥4 weeks.
- Severe Exfoliative Dermatologic Events:
  - Suspected: Treat with high potency topical steroids to affected areas. Treat with oral prednisone or equivalent at an initial dose of 0.5 to 1 mg/kg/day and taper steroid when dermatitis is controlled. Ensure adequate evaluation (eg, urgent dermatology consultation) to confirm etiology and/or exclude other causes.

  - Confirmed: Administer 1 to 2 mg/kg/day IV methylprednisolone or equivalent and taper steroid when dermatitis is controlled.

- Renal Failure or Nephritis:
  - Treat with systemic corticosteroids, oral for Grade 2 (initial dose of 0.5 to 1 mg/kg per day of prednisone or equivalent) and IV for Grade 3-4 (1 to 2 mg/kg per day of prednisone or equivalent).
  - Taper corticosteroids when symptoms improve to Grade ≤1 over ≥4 weeks.
- Adrenal Insufficiency:
  - Start treatment with corticosteroids before other hormone replacement therapy to avoid adrenal crisis (hydrocortisone slowly titrating doses down according to symptoms or prednisone and fludrocortisone titrating up or down based on blood pressure, other symptoms, and laboratory results); patients with severe symptoms may require additional fluids (eg, saline >2 L).
  - Monitor for cortisol level (AM), comprehensive metabolic panel (Na, K, CO_2, glucose), and renin.
  - Ensure adequate evaluation (eg, endocrine consultation).
- Myocarditis:
  - Administer high-dose corticosteroids (1 g/day of IV methylprednisolone) for 3 to 5 days, followed by oral prednisone taper over 4 to 6 weeks based on improvement in cardiac function and biomarkers.
  - If no improvement in 24 hours, consider adding other potent immunosuppressive agents.
  - Ensure adequate evaluation (eg, urgent cardiology consultation) to confirm etiology and/or exclude other causes.
- Severe Neurological Events (Myasthenic Syndrome/Myasthenia Gravis, Guillain-Barré Syndrome, Immune-Related Encephalitis, Transverse Myelitis)
  - Consider high dose corticosteroids and other therapies as needed.
  - It is highly recommended that Investigators discuss any AEs with the Sponsor before using infliximab.
  - Ensure adequate evaluation (eg, neurology consultation).
  - Consider MRI of brain and/or spine depending on symptoms.
  - Consider inpatient management as clinically indicated.
- Uveitis:
  - Urgent ophthalmology consultation.
  - Administer treatment with ophthalmic and systemic prednisone/methylprednisone.

- **Management of Infusion-related Reactions**: An infusion-related reaction is defined as an AE to the infusion of TSR-033 or dostarlimab that occurs during the infusion or within 2 hours of completion of the infusion. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely. Table 3 shows treatment guidelines for patients who experience an infusion-related reaction associated with administration of TSR-033 or dostarlimab.

Table 3: TSR-033 or Dostarlimab Infusion-Related Reaction Treatment Guidelines

CTCAE Grade	Treatment[a]	Premedication at Subsequent Treatment
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 (eg, antihistamines, NSAIDS, narcotics, and/or 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 (eg, from 100 mL/h to 50 mL/h). Otherwise, dosing will be held until symptoms resolve, and the patient should be premedicated for the next scheduled dose. The end of infusion PK sample should always be drawn at the end of the last study medication infusion, regardless if the infusion is slowed or temporarily stopped due to an infusion reaction. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment administration.**	Patient may be premedicated 1.5 hours (±30 minutes) prior to infusion of TSR-033 ±dostarlimab with: -Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). -Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).

Table 3: TSR-033 or Dostarlimab Infusion-Related Reaction Treatment Guidelines (Continued)

CTCAE Grade	Treatment[a]	Premedication at Subsequent Treatment
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication or brief interruption of infusion, or both); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, 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=non-steroidal anti-inflammatory drug; PO=per os (by mouth).

[a] Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

5.7. Continued Access to Study Treatment After Final Analysis

For patients who continue to receive study treatment after the DCO date of the final analysis (see Section 3.3.3), dispensing of study treatment after the clinical study database has closed may be done with a manual resupply option (refer to the Study Reference Manual). Drug accountability data will also be collected at the site. *Note:* There will be no further access to TSR-033 study treatment once the TSR-033 study drug supply expires.

6. ENDPOINTS AND METHODS OF ASSESSMENT

6.1. Safety Endpoints

Safety parameters evaluated during the conduct of the study include DLTs, SAEs, treatment-emergent AEs (TEAEs), irAEs, clinical laboratory assessments (hematology, chemistry, thyroid function, and urinalysis), vital signs, ECGs, physical examination, ECOG PS, and use of concomitant medications.

6.1.1. Definitions

Adverse event: An *AE* 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 *TEAE* will be defined as any new AE that begins, or any pre-existing condition that worsens in severity, after at least 1 dose of study treatment has been administered.

Serious adverse event: An *SAE* 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 (eg, for observation, protocol compliance, elective procedures, or social reasons) 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 SUSAR is serious adverse reaction of which the nature and severity is not consistent with the information about the study drug set out in the IB Reference Safety Information section.

6.1.2. Assessment of Adverse Events

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

6.1.2.1. Intensity

Investigators should assess the severity of AEs according to CTCAE. In general, CTCAE v5.0 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 that 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 (eg, 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 (eg, physical examination, laboratory assessment, ECG, or 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 post treatment or until initiation of alternative anti-cancer therapy, whichever occurs first (see Table 4, Table 5, Table 6, and Table 7 for schedules of events). If an Investigator becomes aware of an SAE after the 90-day follow up period post treatment discontinuation 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 Section 6.1.5. All AEs and SAEs experienced by a patient during the study period, irrespective of the suspected causality, will be monitored until: the AE or SAE has resolved or stabilized, any abnormal laboratory values have returned to baseline or normal levels, there is a satisfactory explanation for the changes observed, the patient is lost to FUP or withdraws consent, or the patient has died.

AEs may be volunteered spontaneously by the study patient, or discovered by the study staff during physical examinations or by asking an open, nonleading question such as: “How have you been feeling since you were last asked?” The Investigator will document the nature of the 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, 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 document 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 (in the medical history section or appropriate page) as well as on the SAE Report Form (medical history section).

6.1.4. Reporting Disease Progression

The event of PD 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 6.1.5. Death due to PD that is consistent with the nature and natural progression of the patient's disease is not reported as AE/SAE.

6.1.5. Reporting of Serious Adverse Events

The Investigator must report all SAEs within 24 hours of becoming aware of the initial SAE or any FUP 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 FUP SAEs. A FUP SAE report must be completed each time an Investigator becomes aware of any additional information regarding the SAE. For the FUP SAE Report Form, the following fields must be completed on each form: FUP 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 FUP SAE Report Form.

Initial and FUP SAE reports and any additional supporting documentation (eg, hospital reports, consultant reports, death certificates, or autopsy reports) 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 SAE forms.

The minimum information required for an initial SAE report is:

- Identification of person sending the report (ie, name and address of Investigator)
- Patient identification (screening 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 (eg, 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 FUP 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.

6.1.5.1. Submission and Distribution of Serious Unexpected Suspected Adverse Reaction Reports

All SAEs that are unexpected and considered by the Investigator or Sponsor to be reasonably associated (related or possibly related) with the use of the investigational study drug(s) are subject to expedited safety reporting to health regulatory agencies. Per regulatory requirements, if an SAE is assessed by TESARO as a SUSAR it will be submitted to the Regulatory Authorities. In addition to this, a copy of the report (Council for International Organizations of Medical Sciences [CIOMS] or MedWatch 3500A) will be distributed to the Investigators/site. A copy of the report will be submitted to the respective Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and Investigators as per local regulation.

Disease progression or AEs related to the underlying disease, as defined in the study protocol, unless resulting in death, should be considered as expected and are excluded from the regulatory requirements for expedited reporting.

TESARO has delegated the reporting of some of the SUSARs reporting duties to a third party. Information about the third parties responsible for SUSAR reporting to Health Authorities, Investigators, IRBs, and IECs is listed in the application documentation submitted to regulatory authorities.

6.1.6. Pregnancy

Pregnancies occurring in patients enrolled in this study must be reported and followed to outcome. If a 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 to the Sponsor.

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 (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or 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 FUP with the patient until delivery or termination of pregnancy, even if the patient was withdrawn from the study or if the 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 6.1.5).

6.1.7. Clinical Laboratory Assessments

The following laboratory variables will be determined in accordance with the schedule of events (see Table 4, Table 5, Table 6, and Table 7). These tests will be performed by the local laboratory at the clinical site.

- CBC:
  - Hb
  - Mean corpuscular volume
  - White blood cell count
  - Platelets
  - 5-part differential white cell count (absolute or percentage)
  - Mean platelet volume (optional, but highly encouraged, especially for patients with high grade thrombocytopenia)
- Coagulation factors:
  - INR
  - aPTT
  - PT
- Chemistry:
  - Sodium
  - Potassium
  - Calcium
  - Magnesium
  - Chloride
  - Glucose (fasting at baseline); baseline may be screening or pre-dose (Dose 1, Day 1)
  - Creatinine and estimated CrCL using Cockcroft-Gault formula (see Appendix 4)
  - Urea or blood urea nitrogen
  - Bicarbonate
  - Amylase
  - Bilirubin (total and direct; in the event that a total bilirubin result >ULN, direct bilirubin will be obtained and recorded in the CRF)
  - Alkaline phosphatase (ALP)
  - AST
  - ALT

  - Total protein
  - Albumin
  - Lactate dehydrogenase
  - Lipase
- Urinalysis:
  - Specific gravity
  - Leukocyte esterase
  - Nitrite
  - Blood
  - Bilirubin
  - Protein
  - Glucose
  - Ketones
  - Urobilinogen
  - Microscopy (if clinically indicated)
- Thyroid panel (ie, TSH, T3 or FT3, and FT4 [or T4 if FT4 is not available], or equivalent tests, where applicable)
- Serum or urine pregnancy testing (women of childbearing potential [WOCBP] only)
- Hepatitis B surface antigen (HBsAg) and hepatitis C virus ribonucleic acid (HCV RNA) testing (screening only if clinically indicated eg, patients with history of IV drug use)

Any laboratory values 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 6.1.5).

6.1.8. Physical Examination and Vital Signs

Complete physical examinations, including height (screening only), weight, and vital signs (BP, pulse, respiratory rate, and temperature) will be performed in accordance with the schedule of events (see Table 4, Table 5, Table 6, and Table 7).

Any physical examination or vital signs assessed as clinically significant should be recorded as an AE or SAE. If any seriousness criteria are met, the event should be recorded and reported according to the SAE reporting process (see Section 6.1.5).

6.1.8.1. Symptom-Directed Physical Examination

Symptom-directed physical exams will be performed throughout the study as clinically indicated.

6.1.9. Electrocardiogram

A standard 12-lead ECG will be performed in accordance with the schedule of events (see Table 4, Table 5, Table 6, and Table 7). Any ECG result assessed as clinically significant should be recorded as an AE or SAE. If any seriousness criteria are met, the event should be recorded and reported according to the SAE reporting process (see Section 6.1.5).

6.1.10. Eastern Cooperative Oncology Group Performance Status

PS will be assessed using the ECOG scale (see Appendix 3) in accordance with the schedule of events (see Table 4, Table 5, Table 6, and Table 7). The same observer should assess PS each time.

6.1.11. Additional Safety Assessments

All patients will undergo ECGs in accordance with the schedule of events (see Table 4, Table 5, Table 6, and Table 7). ECGs 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 any seriousness criteria are met, the event should be recorded and reported according to the SAE reporting process (see Section 6.1.5).

6.1.12. Collection of Safety Information After Final Analysis

For patients who continue to receive study treatment after the DCO date of the final analysis (see Section 3.3.3), the Sponsor will continue to collect safety information including SAEs, AEs leading to discontinuation of study treatment, overdoses, and pregnancies; these events will be reported directly to the Sponsor via paper forms (refer to the Study Reference Manual). The events will be reported per defined time frames as follows:

- SAEs, AEs leading to discontinuation of study treatment, and overdoses will be reported during the treatment period and for up to 90 days after last dose or until initiation of alternative anti-cancer therapy, whichever occurs first.
- Pregnancies will be reported during the treatment period and for up to 150 days after last dose.

Reporting of these events (SAEs, AEs leading to discontinuation of study treatment, overdoses, and pregnancies) will continue to be in accordance with the protocol. Additionally, any SAE that is ongoing at the time of the DCO date of the final analysis must be followed-up to resolution, unless the event is considered by the Investigator as unlikely to resolve or the patient is lost to follow-up. The Sponsor retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the time of the DCO date of the final analysis, if judged necessary.

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 Demographics

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

6.2.3. Cancer History

For disease history the following will be documented:

- Date of first diagnosis
- Tumor type
- Part 2, primary and/or metastatic tumor is known to be MSS as determined locally
- Stage at time of initial diagnosis
- Histology and grade of disease at diagnosis and most recent biopsy if additional biopsy performed
- Information on first anti-cancer treatment:
  - Intent (adjuvant, neoadjuvant, curative, or palliative)
  - Date of start of first treatment
  - Agents used in first treatment
  - Date of last dose of first treatment
- Information on second and subsequent anti-cancer treatments:
  - Intent (adjuvant, neoadjuvant, curative, or palliative)
  - Dates of start of all subsequent treatments
  - Agents used in all subsequent treatments
  - Dates of last dose of all subsequent treatments
- Best response and toxicities for each prior anti-cancer treatment
- Date of recurrence for each prior anti-cancer treatment

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 Concurrent Medications

Previous and concomitant medication will be documented as described in Section 5.6. Medications will be coded using World Health Organization (WHO) 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 TSR-033 will be evalu[CCI]sment of tumor response to treatment according to RECIST v1.1[53] (Appendix 1 and [CCI] [Section 6.3.1.3, Section 6.3.1.4, and Appendix 2]). Serum-based tumor marker data will not be used for defining objective responses or disease progression; however, these can be used for clinical decisions.

Response to treatment will primarily be based on Investigator evaluation of radiographic images. In Part 2, all radiographic images/scans at the time points specified (Table 4, Table 5, Table 6, and Table 7), as well as any unscheduled images/scans, will be collected and stored at a repository for potential 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, as well as brain or other regions known to have disease involvement) should be performed using the same imaging technique 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 MRI, ie when CT is contraindicated or for imaging of the brain. 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 FUP.

Bone scans should be conducted per SOC.

6.3.1.2. Timing of Radiographic Evaluations

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.

Tumor imaging should be performed Q6W (42 ±7 days) for the first 3 assessments and then every 9 (63 ±7 days) weeks thereafter, 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 ±7 days). Imaging should not be delayed for delays in dosing.

Per RECIST v1.1 (see Appendix 1), CR or PR 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, but no later than 35 days, whichever is clinically indicated. Additionally, PD should also be confirmed a minimum of 4 weeks, and up to 9 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).

Continue to perform imaging until whichever of the following occurs:

- The start of new anti-cancer treatment
- Withdrawal of consent
- Death
- End of the study (when responder or discontinuation status for all patients is known)

Patients who discontinue study treatment for reasons other than PD will continue post-treatment imaging studies for disease status FUP at the same frequency as already followed (every 6, 9, or 12 weeks [±7 days] depending on the length of treatment with the study drug) until PD, start of a non-study anti-cancer treatment, withdrawal of consent to study participation, loss to FUP, death, or end of the study.

6.3.1.3. Assessment of Response by RECIST

RECIST v1.1 will be used by the Investigator as the primary measure for assessment of tumor response, date of PD, and as a basis for all protocol guidelines related to disease status. Note that CCI [redacted] 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 1.

CCI [redacted]

CCI [redacted]

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.[54] 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 9 weeks later, see Appendix 2). The Investigator's decision to continue treatment beyond the initial assessment of progression should be based on the patient's overall clinical condition, including PS, clinical symptoms, and laboratory data. A patient may receive TSR-033 treatment while waiting for confirmatory imaging if he or she is clinically stable per the following criteria:

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

Whenever possible, patients should not be discontinued until PD is confirmed.

6.3.2. Efficacy Endpoints

6.3.2.1. Objective Response Rate

The primary efficacy endpoint is ORR for Part 2A, defined as the proportion of patients achieving CR or PR as assessed by the Investigator per RECIST v1.1 (Appendix 1). ORR in Part 1 and Part 2B of the study is a secondary endpoint. Tumor assessments after the initiation of further anti-cancer therapy are excluded for the assessment of best overall response.

CCI [redacted]

6.3.2.2. Duration of Response

DOR will be evaluated as a secondary endpoint in Part 2 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 per RECIST v1.1 (Appendix 1).

CCI [redacted]

6.3.2.3. Disease Control Rate

DCR will be assessed as a secondary endpoint in Part 2 and is defined as the percentage of patients achieving CR, PR, or stable disease (SD) as assessed by the Investigator per RECIST v1.1 (Appendix 1). SD per RECIST v1.1 for a minimum of 12 weeks is necessary for inclusion in evaluation of DCR.

CCI [redacted]

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 TSR-033 and dostarlimab will be collected from patients in both Part 1 and Part 2. Sampling times for blood for PK analysis are detailed in Table 8, Table 9, Table 10, Table 11, and Table 12.

In Part 1, all sampling times are relative to the of the TSR-033 infusion. **The end of infusion sample for TSR-033 must be taken before starting the dostarlimab infusion in Part 1c of the study.** If the end of the dostarlimab infusion is later than 1 hour (±5 minutes) relative to the start of the TSR-033 infusion, an end of infusion sample must be taken for dostarlimab. In Part 2, post-infusion samples are taken at the end of the dostarlimab administration for doses/weeks where TSR-033 and dostarlimab are given in combination (ie, Dose 1, Dose 4, etc.), and at the end of the TSR-033 for doses/weeks where TSR-033 is administered alone (ie, Dose 2, Dose 3, Dose 5, etc.).

In Part 1b, a cohort(s) of up to 6 additional patients may be enrolled in any dose level with DLTs <⅓ of patients to better characterize the PK profile of TSR-033 CCI [redacted] CCI [redacted] In this cohort(s), TSR-033 will be administered on Day 1, Day 29, and Q2W thereafter (without administration of a Day 15 dose). The extended treatment durations in the absence of the second dose on Day 15 enables a better characterization of the terminal phase of the PK profile, which can lead to more accurate calculations of PK parameters (such as $t_{½}$). Additionally, this extended treatment interval will provide additional CCI [redacted] that may

contribute to the determination of the RP2D. The decision regarding which cohort(s) to expand for this evaluation will be determined by the Sponsor and the Investigators.

The serum samples for PK determination will be analyzed using ELISA.

The end of infusion PK sample should always be drawn at the end of the last study medication infusion, regardless if the infusion is slowed or temporarily stopped due to an infusion reaction.

6.4.2. Analysis of Antidrug Antibodies

Serum samples for the determination of anti-TSR-033 antibodies and anti-dostarlimab antibodies will be the same samples collected as for PK. Minimally, ADAs will be analyzed using electrochemiluminescence (ECL) with pre-dose samples from all doses collected and terminal phase samples, as appropriate, from first and sixth doses for Part 1 patients. For all patients, additional samples for ADA determination will be collected upon treatment discontinuation at a safety FUP visit (ie, approximately 30 and 90 days after the last dose of TSR-033 or dostarlimab, or both, to coincide with the safety FUP visits).

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

7. STUDY CONDUCT

7.1. Schedules of Events

Schedules of events and procedures are provided in Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, Table 12, Table 13, Table 14, Table 15, Table 16, Table 17, and Table 18.

Patients who continue to receive study treatment after the DCO date of the final analysis (see Section 3.3.3) will be monitored and receive follow-up care in accordance with standard local clinical practice. Assessments will revert to the standard of care at a patient's particular study site and only SAEs, AEs leading to discontinuation of study treatment, overdoses, and pregnancies will be reported directly to the Sponsor via paper forms (see Section 6.1.12; refer to the Study Reference Manual for further details on reporting using paper forms).

7.1.1. Use of Standard of Care Assessments for Screening

In some cases, clinical assessments performed prior to obtaining informed consent may be used to qualify the patient for the study, providing these assessments are performed within 21 days prior to the first dose of study treatment (within 28 days for radiologic assessments). These include radiological examinations, ECGs, physical examinations, vital signs, hematology, chemistry, coagulation studies, or urinalysis, which may be considered as part of normal SOC. In these cases, repeat assessments may not be necessary prior to enrollment unless individual parameters require further study or confirmation and are clinically appropriate.

Table 4: Schedule of Clinical Events: TSR-033 Monotherapy, Part 1a and Part 1b (Q2W)

Visit/Dose:	Screening	Dose 1					Dose 2		Subsequent Doses	EOT[a]	Safety FUP[b]	Survival FUP
Day: Procedure (Protocol Section):	-21 to -1	1	2	3	5 (±24 hr)	8 (±24 hr)	1 (±24 hr)	8 (±24 hr)	Dose n, Day 1		(Every 30 and 90 ±7 Days)	(Every 90 ±14 Days)
Informed consent (Section 9.7)	X											
Inclusion/exclusion criteria review (Sections 4.1 and 4.2)	X											
Confirm that patient continues to satisfy eligibility criteria (Sections 4.1 and 4.2)		X										
Demographics (Section 6.2)	X											
Cancer, Medical, Surgical and Medication history (Sections 6.2.3, 6.2.4, and 6.2.5)	X											
Tumor assessment (RECIST v1.1 and CCI (Section 6.3.1, Appendix 1, and Appendix 2)	X								Per Section 6.3.1.2	X[c]		
CBC with 5-part differential – **Part 1a** (Section 6.1.7)	X	X[d]	X	X	X	X	X	X	X[d]	X	X	
CBC with 5-part differential – **Part 1b** (Section 6.1.7)	X	X[d]	X	X	X	**Days 8, 15, & 22**	X	X	X[d]	X	X	
Chemistry–**Part 1a** (Section 6.1.7)	X	X[d]	X			X	X	X	X[d]	X	X	
Chemistry–**Part 1b** (Section 6.1.7)	X	X[d]	X			**Days 8, 15, & 22**	X	X	X[d]	X	X	

Table 4: Schedule of Clinical Events: TSR-033 Monotherapy, Part 1a and Part 1b (Q2W) (Continued)

Visit/Dose:	**Screening**	**Dose 1**					**Dose 2**		**Subsequent Doses**	**EOT[a]**	**Safety FUP[b]**	**Survival FUP**
Day: **Procedure (Protocol Section):**	**-21 to -1**	**1**	**2**	**3**	**5 (±24 hr)**	**8 (±24 hr)**	**1 (±24 hr)**	**8 (±24 hr)**	**Dose n, Day 1**		**(Every 30 and 90 ±7 Days)**	**(Every 90 ±14 Days)**
Coagulation (Section 6.1.7)	X								Per SOC for patients on anticoagulant therapy			
Pregnancy test in WOCBP only (Section 6.1.7)	Within 72 hours of Dose 1	Every 3 months during study treatment								X	X	
HBV/HCV test (if clinically indicated; eg, history of IV drug use) (Section 6.1.7)	X											
Urinalysis (Section 6.1.7)	X	X[d]					X		X[d]	X	X	
Serum-based tumor markers (eg, CEA) (Section 3.3.1.3)	X	X[d]							X[d]	X		
Thyroid panel (Section 6.1.7)	X	Every 6 weeks and if clinically indicated								X		
12-Lead ECG (Section 6.1.9)	Patients will undergo ECG monitoring at screening, pre-dose on Dose 1, Day 1, every 28 days thereafter while on study treatment, at the EOT visit, and at any time it is clinically indicated											
Complete PE (Section 6.1.8)	X									X	X	
Symptom-directed PE (Section 6.1.8.1)		Throughout the study as clinically indicated										
Vital signs, height (at screening only), and weight–**Part 1a** (Sections 5.2.1 and 6.1.8)	X	X	X	X	X	X	X	X	X	X		

Table 4: Schedule of Clinical Events: TSR-033 Monotherapy, Part 1a and Part 1b (Q2W) (Continued)

Visit/Dose:	Screening	Dose 1					Dose 2		Subsequent Doses	EOT[a]	Safety FUP[b]	Survival FUP
Day: Procedure (Protocol Section):	-21 to -1	1	2	3	5 (±24 hr)	8 (±24 hr)	1 (±24 hr)	8 (±24 hr)	Dose n, Day 1		(Every 30 and 90 ±7 Days)	(Every 90 ±14 Days)
Vital signs, height (at screening only), and weight–**Part 1b** (Sections 5.2.1 and 6.1.8)	X	X	X	X	X	Days 8, 15, & 22	X	X	X	X		
ECOG PS (Appendix 3)	X								Pre-dose	X		
AE monitoring (Sections 6.1.2, 6.1.3, 6.1.4, and 6.1.5)	Collected from the time of signed informed consent (Day -21 to Day -1) and at all study visits through the 90-day SFU, or until initiation of alternative anti-cancer therapy, whichever occurs first											
Concomitant medications (Sections 5.6 and 6.2.5)	Collected at screening and at all study visits through the 30-day SFU, or until initiation of alternative anti-cancer therapy, whichever occurs first											
TSR-033 administered–**Part 1a** (Sections 3.1.3.1, 5.2, and the Pharmacy Manual)		X					Day 15		Every 14 days (±1 day)			
TSR-033 administered–**Part 1b** (Sections 3.1.3.2, 5.2, and the Pharmacy Manual)		X					Day 29		Every 14 days (±1 day)			
Post-infusion, 4-hour observation period (Section 5.2.1)		X					X					
Survival assessment and anti-cancer treatments (Section 3.3.1.6)												Via telephone

Abbreviations: AE=adverse event; CBC=complete blood count; CEA=carcinoembryonic antigen; CRC=colorectal cancer; 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; hr=hours; CCI ; IV=intravenous; MRI=magnetic resonance imaging; PD=progressive disease; PE=physical examination; PS=performance status; Q2W=every 2 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; SFU=study follow up; SOC=standard of care; WOCBP=women of child bearing potential.

[a] The EOT visit will occur within 7 days of the decision to discontinue study treatment for any reason.

[b] Safety FUP visit should be conducted 30 (±7) and 90 (±7) days after last study drug dose. Should the first dose of a new anti-cancer therapy occur within 14 days of the decision to discontinue study treatment, all assessments required for the Safety FUP visit should occur at the EOT visit, and this visit will be

considered the Safety FUP visit. If the first dose of the new anti-cancer therapy occurs >14 days after the decision to discontinue study, the Safety FUP visit will occur 30 ±7 days after the last dose of the study drug, or at the start of any new anti-cancer therapy, whichever occurs first.

[c] Tumor assessment per RECIST v1.1 and [redacted] via CT or MRI (chest, abdomen, and pelvis [as well as brain or other regions known to have disease involvement]) are required within 28 days prior to Dose 1, Day 1. Subsequent imaging should be performed every 6 weeks (42 ±7 days) for the first 3 assessments and every 9 weeks (63 ±7 days) thereafter while on study treatment, or more frequently if clinically indicated and at the time of suspected PD. After 1 year, tumor assessments may be performed every 12 weeks (84 ±7 days). Imaging should not be delayed for delays in dosing. If applicable, testing of serum-based tumor markers (eg, CEA for patients with CRC) should coincide approximately (±5 days) with radiographic tumor assessments. The tumor imaging for confirmation of response may be performed at the earliest 28 days after the first indication of response, but no later than 35 days, whichever is clinically indicated. The subsequent scan after the confirmatory scan should be obtained per the original schedule. Clinically stable patients should not be discontinued until progression is confirmed (Section 6.3.1). Patients who discontinue study treatment for reasons other than PD will continue post-treatment imaging studies as described in Section 6.3.1.2.

[d] If screening laboratory testing (CBC, chemistry, serum-based tumor markers, and urinalysis) performed within 72 hours prior to or on Dose 1, Day 1, repeat testing is not required. Laboratory testing (CBC, chemistry, serum-based tumor markers, and urinalysis) is allowed up to 24 hours prior to TSR-033 infusion during the study. Pre-dose test results must be reviewed prior to dosing. Starting with Dose 5 of TSR-033, laboratory testing is only to be performed on odd numbered doses (ie, every 28 days).

Table 5: Schedule of Clinical Events: TSR-033 + Dostarlimab Combination Therapy, Part 1c (Q3W)

Visit/Dose:	Screening	Dose 1					Dose 2		Subsequent Doses	EOT[a]	Safety FUP[b]	Survival FUP
Day: Procedure (Protocol Section):	-21 to -1	1	2	3	5 (±24 hr)	8&15 (±24 hr)	1 (±24 hr)	8&15 (±24 hr)	Dose n, Day 1		(Every 30 and 90 ±7 Days)	(Every 90 ±14 Days)
Informed consent (Section 9.7)	X											
Inclusion/exclusion criteria review (Sections 4.1 and 4.2)	X											
Confirm that patient continues to satisfy eligibility criteria (Sections 4.1 and 4.2)		X										
Demographics (Section 6.2)	X											
Cancer, Medical, Surgical and Medication history (Sections 6.2.3, 6.2.4, and 6.2.5)	X											
Tumor assessment (RECIST and CCI (Section 6.3.1, Appendix 1, and Appendix 2)	X								Per Section 6.3.1.2	X[c]		
CBC with 5-part differential (Section 6.1.7)	X	X[d]	X	X	X	X	X	X	X[d]	X	X	
Chemistry (Section 6.1.7)	X	X[d]	X			X	X	X	X[d]	X	X	
Coagulation (Section 6.1.7)	X								Per SOC for patients on anticoagulant therapy			
Pregnancy test for WOCBP only (Section 6.1.7)	Within 72 hours of Dose 1	Every 3 months during study treatment								X	X	

Table 5: Schedule of Clinical Events: TSR-033 + Dostarlimab Combination Therapy, Part 1c (Q3W) (Continued)

Visit/Dose:	**Screening**	**Dose 1**					**Dose 2**		**Subsequent Doses**	**EOT[a]**	**Safety FUP[b]**	**Survival FUP**
Day: **Procedure (Protocol Section):**	**-21 to -1**	**1**	**2**	**3**	**5 (±24 hr)**	**8&15 (±24 hr)**	**1 (±24 hr)**	**8&15 (±24 hr)**	**Dose n, Day 1**		**(Every 30 and 90 ±7 Days)**	**(Every 90 ±14 Days)**
HBV/HCV test (if clinically indicated; eg, history of IV drug use) (Section 6.1.7)	X											
Urinalysis (Section 6.1.7)	X	X[d]					X		X[d]	X	X	
Serum-based tumor markers (eg, CEA) (Section 3.3.1.3)	X	X[d]							X[d]	X		
Thyroid panel (Section 6.1.7)	X	Every 6 weeks and if clinically indicated								X		
ECG (Section 6.1.9)	Patients will undergo ECG monitoring at screening, pre-dose on Dose 1, Day 1, every 28 days thereafter while on study treatment, at the EOT visit, and at any time it is clinically indicated											
Complete PE (Section 6.1.8)	X									X	X	
Symptom-directed PE (Section 6.1.8.1)		Throughout the study as clinically indicated										
Vital signs, height (at screening only), and weight (Sections 5.2.1 and 6.1.8)	X	X	X	X	X	X	X	X	X	X		
ECOG PS (Appendix 3)	X								Pre-dose	X		
AE monitoring (Sections 6.1.2, 6.1.3, 6.1.4, and 6.1.5)	Collected from the time of signed informed consent (Day -21 to Day -1) and at all study visits through the 90-day SFU, or until initiation of alternative anti-cancer therapy, whichever occurs first											
Concomitant medications (Sections 5.6 and 6.2.5)	Collected at screening and at all study visits through the 30-day SFU, or until initiation of alternative anti-cancer therapy, whichever occurs first											
TSR-033 + dostarlimab administered (Section 5.2)		X					Day 22		Every 21 days			

Table 5: Schedule of Clinical Events: TSR-033 + Dostarlimab Combination Therapy, Part 1c (Q3W) (Continued)

Visit/Dose:	Screening	Dose 1					Dose 2		Subsequent Doses	EOT[a]	Safety FUP[b]	Survival FUP
Day: Procedure (Protocol Section):	-21 to -1	1	2	3	5 (±24 hr)	8&15 (±24 hr)	1 (±24 hr)	8&15 (±24 hr)	Dose n, Day 1		(Every 30 and 90 ±7 Days)	(Every 90 ±14 Days)
Post-infusion, 4-hour observation period (Section 5.2.1)		X					X					
Survival assessment and anti-cancer treatments (Section 3.3.1.6)												Via telephone

Abbreviations: AE=adverse event; CBC=complete blood count; CEA=carcinoembryonic antigen; CRC=colorectal cancer; 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; hr=hours; CCI [redacted] IV=intravenous; MRI=magnetic resonance imaging; PD=progressive disease; PE=physical examination; PS=performance status; Q3W=every 3 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; SFU=study follow up; SOC=standard of care.

[a] The EOT visit will occur within 7 days of the decision to discontinue study treatment for any reason.

[b] Safety FUP visit should be conducted 30 (±7) and 90 (±7) days after last study drug dose. Should the first dose of a new anti-cancer therapy occur within 14 days of the decision to discontinue study treatment, all assessments required for the Safety FUP visit should occur at the EOT visit, and this visit will be considered the Safety FUP visit. If the first dose of the new anti-cancer therapy occurs >14 days after the decision to discontinue study, the Safety FUP visit will occur 30 ±7 days after the last dose of the study drug, or at the start of any new anti-cancer therapy, whichever occurs first.

[c] Tumor assessment per RECIST v1.1 and CCI [redacted] via CT or MRI (chest, abdomen, and pelvis [as well as brain or other regions known to have disease involvement]) are required within 28 days prior to Dose 1, Day 1. Subsequent imaging should be performed every 6 weeks (42 ±7 days) for the first 3 assessments and every 9 weeks (63 ±7days) thereafter while on study treatment, or more frequently if clinically indicated and at the time of suspected PD. After 1 year, tumor assessments may be performed every 12 weeks (84 ±7 days). Imaging should not be delayed for delays in dosing. If applicable, testing of serum-based tumor markers (eg, CEA for patients with CRC) should coincide approximately (±5 days) with radiographic tumor assessments. The tumor imaging for confirmation of response may be performed at the earliest 28 days after the first indication of response, but no later than 35 days, whichever is clinically indicated. The subsequent scan after the confirmatory scan should be obtained per the original schedule. Clinically stable patients should not be discontinued until progression is confirmed (Section 6.3.1). Patients who discontinue study treatment for reasons other than PD will continue post-treatment imaging studies as described in Section 6.3.1.2.

[d] If screening laboratory testing (CBC, chemistry, serum-based tumor markers, and urinalysis) performed within 72 hours prior to or on Dose 1, Day 1, repeat testing is not required. Laboratory testing (CBC, chemistry, serum-based tumor markers, and urinalysis) is allowed up to 24 hours prior to TSR-033 infusion during the study. Pre-dose test results must be reviewed prior to dosing. Starting with Dose 5 of TSR-033, laboratory testing is only to be performed on odd numbered doses (ie, every 28 days).

Table 6: Schedule of Clinical Events: Part 2A

Visit/Dose:	Screening	Dose 1	Subsequent Doses	EOT (Within 7 Days of Decision to Discontinue)	Safety FUP[a]	FUP Assessments
Day: Procedure (Protocol Section):	-28 to -1	1	Dose n, Day 1 (±24 hr)		(Every 30 and 90 ±7 Days)	(Every 90 ±14 Days)
Informed consent (Section 9.7)	X					
Inclusion/exclusion criteria review (Sections 4.1 and 4.2)	X					
Confirmation that patient continues to satisfy eligibility criteria (Sections 4.1 and 4.2)		X				
Demographics (Section 6.2)	X					
Cancer, Medical, Surgical and Medication history (Sections 6.2.3, 6.2.4, and 6.2.5)	X					
Tumor assessment (RECIST and [CCI redacted] (Section 6.3.1, Appendix 1, and Appendix 2)	X		X[c]	X[b]		
CBC with 5-part differential (Section 6.1.7)	X	X[d]	X[d]	X	X	
Chemistry (Section 6.1.7)	X	X[d]	X[d]	X	X	
Coagulation factors (Section 6.1.7)	X		Per SOC for patients on anticoagulant therapy			

Table 6: Schedule of Clinical Events: Part 2A (Continued)

Visit/Dose:	**Screening**	**Dose 1**	**Subsequent Doses**	**EOT (Within 7 Days of Decision to Discontinue)**	**Safety FUP[a]**	**FUP Assessments**
Day: **Procedure (Protocol Section):**	**-28 to -1**	**1**	**Dose n, Day 1 (±24 hr)**		**(Every 30 and 90 ±7 Days)**	**(Every 90 ±14 Days)**
Pregnancy test for WOCBP only (Section 6.1.7)	Within 72 hours of Dose 1		Every 3 months during study treatment	X	X	
HBV/HCV test (Section 6.1.7)	X					
Serum-based tumor markers (eg, CEA) (Section 3.3.1.3)	X	X[d]	X[d]	X		
Urinalysis (Section 6.1.7)	X	X[d]	X[d]	X	X	
Thyroid panel (Section 6.1.7)	X	Every 6 weeks (ie Dose 1, 4, 7, etc.) and if clinically indicated		X		
ECG (Section 6.1.9)	Patients will undergo ECG monitoring at screening, pre-dose on Dose 1, Day 1, every 28 days thereafter while on study treatment, at the EOT visit, and at any time it is clinically indicated					
Physical examination (Section 6.1.8)	X			X	X	
Symptom-directed PE (Section 6.1.8.1)		Throughout the study as clinically indicated				
Vital signs, height (at screening only), and weight (Sections 5.2.1 and 6.1.8)	X	X	X	X		
ECOG-PS (Appendix 3)	X		Pre-dose	X		
AE monitoring (Sections 6.1.3, 6.1.4 and 6.1.5)	Collected from the time of signed informed consent (Day -28 to Day -1) and at all study visits through the 90-day SFU, or until initiation of alternative anti-cancer therapy, whichever occurs first					
Concomitant medications (Section 5.6 and 6.2.5)	Collected at screening and at all study visits through the 30-day SFU, or until initiation of alternative anti-cancer therapy, whichever occurs first					

Table 6: Schedule of Clinical Events: Part 2A (Continued)

Visit/Dose:	Screening	Dose 1	Subsequent Doses	EOT (Within 7 Days of Decision to Discontinue)	Safety FUP[a]	FUP Assessments
Day: Procedure (Protocol Section):	-28 to -1	1	Dose n, Day 1 (±24 hr)		(Every 30 and 90 ±7 Days)	(Every 90 ±14 Days)
TSR-033 administration Q2W (Section 5.2)		X	X			
Dostarlimab administration Q6W (Section 5.2)		X	Every third dose (Dose 1, 4, 7, etc.)			
Post-infusion, 2-hour observation period (Section 5.2.1)		X	X[e]			
Survival assessment and anti-cancer treatments (Section 3.3.1.6)						Via telephone

Abbreviations: AE=adverse event; CBC=complete blood count; CEA=carcinoembryonic antigen; CRC=colorectal cancer; 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; IR=infusion reaction; CCI ; IV=intravenous; MRI=magnetic resonance imaging; PD=progressive disease; PE=physical examination; PS=performance status; RECIST=Response Evaluation Criteria in Solid Tumors; SFU=study follow up; SOC=standard of care.

[a] Safety FUP visit should be conducted 30 (±7) and 90 (±7) days after last study drug dose. Should the first dose of a new anti-cancer therapy occur within 14 days of the decision to discontinue study treatment, all assessments required for the Safety FUP visit should occur at the EOT visit, and this visit will be considered the Safety FUP visit. If the first dose of the new anti-cancer therapy occurs >14 days after the decision to discontinue study, the Safety FUP visit will occur 30 ±7 days after the last dose of the study drug, or at the start of any new anti-cancer therapy, whichever occurs first.

[b] Tumor assessment per RECIST v1.1 and CCI via CT or MRI (chest, abdomen, and pelvis [as well as brain or other regions known to have disease involvement]) are required within 28 days prior to Dose 1, Day 1. Subsequent imaging should be performed every 6 weeks (42 ±7 days) for the first 3 assessments and every 9 weeks (63 ±7days) thereafter while on study treatment, or more frequently if clinically indicated and at the time of suspected PD. After 1 year, tumor assessments may be performed every 12 weeks (84 ±7 days). Imaging should not be delayed for delays in dosing. Testing of serum-based tumor markers (eg, CEA for patients with CRC) should coincide approximately (±5 days) with radiographic tumor assessments. The tumor imaging for confirmation of response may be performed at the earliest 28 days after the first indication of response, but no later than 35 days, whichever is clinically indicated. The subsequent scan after the confirmatory scan should be obtained per the original schedule. Clinically stable patients should not be discontinued until progression is confirmed (Section 6.3.1). Patients who discontinue study treatment for reasons other than PD will continue post-treatment imaging studies as described in Section 6.3.1.2.

[c] Dose 4, 7, and 10 (±1 week); then every 9 (±1) weeks thereafter (63 ±7days).

[d] If screening laboratory testing (CBC, chemistry, serum-based tumor markers, and urinalysis) performed within 72 hours prior to or on Dose 1, Day 1, repeat testing is not required. Laboratory testing (CBC, chemistry, serum-based tumor markers, and urinalysis) is allowed up to 24 hours prior to TSR-033 infusion

during the study. Pre-dose test results must be reviewed prior to dosing. Starting with Dose 5 of TSR-033, laboratory testing is only to be performed on odd numbered doses (ie, every 28 days).

[e] Should no IRs occur during the 2-hour observation period for Dose 1, observation can be reduced to 1 hour for Dose 2, then to 30 minutes for all doses thereafter. If an IR does occur, patients must be observed for the full 2 hours post dose until no further IRs are observed.

Table 7: Schedule of Clinical Events: Part 2B (Cohorts B1 and B2)

Visit/Dose:	Screening	Dose 1		Subsequent Doses		EOT (Within 7 Days of Decision to Discontinue)	Safety FUP[a]	FUP Assessments
Day: Procedure (Protocol Section):	-28 to -1	1	3	Dose n, Day 1 (±24 hr)	Dose n, Day 3		(Every 30 and 90 ±7 Days)	(Every 90 ±14 Days)
Informed consent (Section 9.7)	X							
Inclusion/exclusion criteria review (Sections 4.1 and 4.2)	X							
Confirmation that patient continues to satisfy eligibility criteria (Sections 4.1 and 4.2)		X						
Demographics (Section 6.2)	X							
Cancer, Medical, Surgical and Medication history (Sections 6.2.3, 6.2.4, and 6.2.5)	X							
Tumor assessment (RECIST and [CCI redacted] (Section 6.3.1, Appendix 1, and Appendix 2)	X			X[c]		X[b]		
CBC with 5-part differential (Section 6.1.7)	X	X[d]		X[d]		X	X	
Chemistry (Section 6.1.7)	X	X[d]		X[d]		X	X	
Coagulation factors (Section 6.1.7)	X			Per SOC for patients on anticoagulant therapy				

Table 7: Schedule of Clinical Events: Part 2B (Cohorts B1 and B2) (Continued)

Visit/Dose:	**Screening**	**Dose 1**		**Subsequent Doses**		**EOT (Within 7 Days of Decision to Discontinue)**	**Safety FUP[a]**	**FUP Assessments**
Day: **Procedure (Protocol Section):**	**-28 to -1**	**1**	**3**	**Dose n, Day 1 (±24 hr)**	**Dose n, Day 3**		**(Every 30 and 90 ±7 Days)**	**(Every 90 ±14 Days)**
Pregnancy test for WOCBP only (Section 6.1.7)	Within 72 hours of Dose 1			Every 3 months during study treatment		X	X	
HBV/HCV test (Section 6.1.7)	X							
Serum-based tumor markers (eg, CEA) (Section 3.3.1.3)	X	X[d]		X[d]		X		
Urinalysis (Section 6.1.7)	X	X[d]		X[d]		X	X	
Thyroid panel (Section 6.1.7)	X	Every 6 weeks (ie, Dose 1, 4, 7, etc.) and if clinically indicated				X		
ECG (Section 6.1.9)	Patients will undergo ECG monitoring at screening, pre-dose on Dose 1, Day 1, every 28 days thereafter while on study treatment, at the EOT visit, and at any time it is clinically indicated							
Physical examination (Section 6.1.8)	X					X	X	
Symptom-directed PE (Section 6.1.8.1)		Throughout the study as clinically indicated						
Vital signs, height (at Screening only), and weight (Sections 5.2.1 and 6.1.8)	X	X		X		X		
ECOG PS (Appendix 3)	X			Pre-dose		X		
AE monitoring (Sections 6.1.3, 6.1.4, and 6.1.5)	Collected from the time of signed informed consent (Day -28 to Day -1) and at all study visits through the 90-day SFU, or until initiation of alternative anti-cancer therapy, whichever occurs first							

Table 7: Schedule of Clinical Events: Part 2B (Cohorts B1 and B2) (Continued)

Visit/Dose:	Screening	Dose 1		Subsequent Doses		EOT (Within 7 Days of Decision to Discontinue)	Safety FUP	FUP Assessments
Day: Procedure (Protocol Section):	-28 to -1	1	3	Dose n, Day 1	Dose n, Day 3		(Every 30 and 90 ±7 Days)	(Every 90 ±14 Days)
Concomitant medications (Section 5.6 and 6.2.5)	Collected at screening and at all study visits through the 30-day SFU, or until initiation of alternative anti-cancer therapy, whichever occurs first							
Bevacizumab and mFOLFOX6 (Cohort B1) or FOLFIRI (Cohort B2) administration Q2W (Section 5.2)		X		X				
TSR-033 administration Q2W (Section 5.2)			X		X			
Dostarlimab administration Q6W (Section 5.2)			X		Every third dose (Dose 1, 4, 7, etc.)			
Post-infusion, 2-hour observation period (Section 5.2.1)			X		X[e]			
Survival assessment and anti-cancer treatments (Section 3.3.1.6)								Via telephone

Abbreviations: AE=adverse event; CBC=complete blood count; CEA=carcinoembryonic antigen; CRC=colorectal cancer; 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; IR=infusion reaction; CCI [redacted], IV=intravenous; MRI=magnetic resonance imaging; PD=progressive disease; PE=physical examination; PS=performance status; RECIST=Response Evaluation Criteria in Solid Tumors; SFU=study follow up; SOC=standard of care.

[a] Safety FUP visit should be conducted 30 (±7) and 90 (±7) days after last study drug dose. Should the first dose of a new anti-cancer therapy occur within 14 days of the decision to discontinue study treatment, all assessments required for the Safety FUP visit should occur at the EOT visit, and this visit will be considered the Safety FUP visit. If the first dose of the new anti-cancer therapy occurs >14 days after the decision to discontinue study, the Safety FUP visit will occur 30 ±7 days after the last dose of the study drug, or at the start of any new anti-cancer therapy, whichever occurs first.

[b] Tumor assessment per RECIST v1.1 and CCI [redacted] via CT or MRI (chest, abdomen, and pelvis [as well as brain or other regions known to have disease involvement]) are required within 28 days prior to Dose 1, Day 1. Subsequent imaging should be performed every 6 weeks (42 ±7 days) for the first 3 assessments and every 9 weeks (63 ±7days) thereafter while on study treatment, or more frequently if clinically indicated and at the time of suspected PD. After

1 year, tumor assessments may be performed every 12 weeks (84 ±7 days). Imaging should not be delayed for delays in dosing. Testing of serum-based tumor markers (eg, CEA for patients with CRC) should coincide approximately (±5 days) with radiographic tumor assessments. The tumor imaging for confirmation of response may be performed at the earliest 28 days after the first indication of response, but no later than 35 days, whichever is clinically indicated. The subsequent scan after the confirmatory scan should be obtained per the original schedule. Clinically stable patients should not be discontinued until progression is confirmed (Section 6.3.1). Patients who discontinue study treatment for reasons other than PD will continue post-treatment imaging studies as described in Section 6.3.1.2.

[c] Dose 4, 7, and 10 (±1 week); then every 9 (±1) weeks thereafter (63 ±7days).

[d] If screening laboratory testing (CBC, chemistry, serum-based tumor markers, and urinalysis) performed within 72 hours prior to or on Dose 1, Day 1, repeat testing is not required. Laboratory testing (CBC, chemistry, serum-based tumor markers, and urinalysis) is allowed up to 24 hours prior to Day 1 of the dosing cycle during the study. Pre-dose test results must be reviewed prior to dosing. Starting with Dose 5 of TSR-033, laboratory testing is only to be performed on odd numbered doses (ie, every 28 days).

[e] Should no IRs occur during the 2-hour observation period for Dose 1, observation can be reduced to 1 hour for Dose 2, then to 30 minutes for all doses thereafter. If an IR does occur, patients must be observed for the full 2 hours post dose until no further IRs are observed.

Table 8: Sampling Schedule for Pharmacokinetic and ADA Analysis: Part 1a (Q2W)

Visit/Dose:	**Dose 1**					**Doses 2–5**	**Dose 6**					**Dose 7**	**Doses ≥8[a]**	**EOT**	**Safety FUP[b]**
Day: **Time Relative to Start of TSR-033 30-minute IV Infusion:**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 8**	**Day 1**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 8**	**Day 1**	**Day 1**		**(Every 30 and 90 ±7 Days)**
Pre-dose (within 30 min)	X					X	X					X	X		
0.25 hr (±5 min)	X					X	X								
0.5 hr (±5 min)	X					X	X						X		
1.5 hr (±5 min)	X						X								
3 hr (±5 min)	X						X								
24 hr (Day 2 ±2 hr)		X						X							
48 hr (Day 3 ±4 hr)			X						X						
96 hr (Day 5 ±24 hr)				X						X					
168 hr (Day 8 ±24 hr)					X						X				
EOT														X	
FUP															X

Abbreviations: ADA=antidrug antibody; EOT=end of treatment; FUP=follow up; hr=hours; IV=intravenous; min=minutes; Q2W=every 2 weeks.

[a] Every other dose (eg, Dose 8, 10, 12, etc.).

[b] For ADA sample collection, this sample collection time will coincide with the safety FUP visits.

Table 9: Sampling Schedule for Additional Pharmacokinetic and ADA Analysis: Part 1b (Q2W)

Visit/Dose:	**Dose 1**							**Doses 2[a]–5**	**Dose 6**					**Dose 7**	**Doses ≥8[b]**	**EOT**	**Safety FUP[c]**
Day: **Time Relative to Start of TSR-033 30-minute IV Infusion:**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 8**	**Day 1**	**Day 1**		**(Every 30 and 90 ±7 Days)**
Pre-dose (w/in 30 min)	X							X	X					X	X		
0.25 hr (±5 min)	X							X	X								
0.5 hr (±5 min)	X							X	X						X		
1.5 hr (±5 min)	X								X								
3 hr (±5 min)	X								X								
24 hr (Day 2 ±2 hr)		X								X							
48 hr (Day 3 ±4 hr)			X								X						
96 hr (Day 5 ±24 hr)				X								X					
168 hr (Day 8 ±24 hr)					X								X				
336 hr (Day 15 ±24 hr)						X											
504 rh (Day 22 ±24 hr)							X[d]										
EOT																X	
FUP																	X

Abbreviations: ADA=antidrug antibody; EOT=end of treatment; FUP=follow up; hr=hours; IV=intravenous; min=minutes; Q2W=every 2 weeks; w/in=within.

[a] The second dose will be given 4 weeks after Dose 1 (on Day 29).

[b] Every other dose (ie, Dose 8, 10, 12, etc.).

[c] For ADA sample collection. This sample collection time will coincide with the safety FUP visits.

[d] Pre-dose (Dose 2).

Table 10: Sampling Schedule for Pharmacokinetic and ADA Analysis: Part 1c (Q3W)

Visit/Dose:	**Dose 1**						**Doses 2-5**	**Dose 6**						**Dose 7**	**Doses ≥8[a]**	**EOT**	**Safety FUP[b]**
Day: **Time Relative to Start of TSR-033 30-minute IV Infusion:**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 1**		**(Every 30 and 90 ±7 Days)**
Pre-dose (w/in 30 min)	X						X[c]	X						X[d]	X		
0.25 hr (±5 min)	X						X	X									
0.5 hr (±5 min)[b,d]	X[d]						X	X[d]							X[d,e]		
1.0 hr (±5min)	X						X	X							X[c]		
1.5 hr (±5 min)	X							X									
3 hr (±5 min)	X							X									
24 hr (Day 2 ±2 hr)		X							X								
48 hr (Day 3 ±4 hr)			X							X							
96 hr (Day 5 ±24 hr)				X							X						
168 hr (Day 8 ±24 hr)					X							X					
336 hr (Day 15 ±24 hr)						X							X				
EOT																X	
FUP																	X

Abbreviations: ADA=antidrug antibody; EOT=end of treatment; FUP=follow up; hr=hours; IV=intravenous; min=minutes; Q3W=every 3 weeks; w/in=within.

[a] Every other dose (Dose 8, 10, 12, etc.).

[b] For ADA sample collection. This sample collection time will coincide with the safety FUP visits.

[c] If the end of infusion for dostarlimab is later than 1.0 hr ±5 min relative to the start of TSR-033 infusion, an end of infusion sample must be taken for dostarlimab.

[d] **Important**: End of infusion sample for TSR-033, must be taken before starting the dostarlimab infusion.

[e] Pre-dose.

Table 11: Sampling Schedule for Pharmacokinetic and ADA Analysis: Part 2A (Q2W)

Visit/Dose:	**Dose 1**	**Dose 2**	**Dose 3**	**Dose 4**	**Dose 5**	**Dose 6**	**Doses ≥8**	**EOT**	**Safety FUP**
Day: **Timepoint:**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**		**(Every 30 and 90 ±7 Days)**
Pre-dose (within 30 min)	X	X	X	X	X	X	X[a]		
End of infusion (±5 min)[b]	X	X	X	X	X	X			
EOT								X	
FUP[c]									X

Abbreviations: ADA=antidrug antibody; EOT=end of treatment; FUP=follow-up; hr=hours; min=minutes; Q2W=every 2 weeks.

[a] Every other dose (Dose 8, 10, 12, etc, regardless if TSR-033 is administered alone or in combination with dostarlimab).

[b] End of infusion of the last investigational drug, ie, on days when TSR-033 is administered alone, the draw is post end of TSR-033 infusion (Dose 2, Dose 3, Dose 5, Dose 6, etc), and when TSR-033 is given in combination with dostarlimab, the draw should be taken at the end of the dostarlimab infusion (Dose 1, Dose 4, etc). The end of infusion PK sample should always be drawn at the end of the last study medication infusion, regardless if the infusion is slowed or temporarily stopped due to an infusion reaction.

[c] For ADA sample collection. This sample collection time will coincide with the safety follow up visits.

Table 12: Sampling Schedule for Pharmacokinetic and ADA Analysis: Part 2B (Cohorts B1 and B2) (Q2W)

Visit/Dose:	**Dose 1**	**Dose 2**	**Dose 3**	**Dose 4**	**Dose 5**	**Dose 6**	**Doses ≥8**	**EOT**	**Safety FUP**
Day: **Timepoint:**	**Day 3**	**Day 3**	**Day 3**	**Day 3**	**Day 3**	**Day 3**	**Day 3**		**(Every 30 and 90 ±7 Days)**
Pre-dose (within 30 min)	X	X	X	X	X	X	X[a]		
End of infusion (±5 min)[b]	X	X	X	X	X	X	X[a]		
EOT								X	
FUP[c]									X

Abbreviations: ADA=antidrug antibody; EOT=end of treatment; FUP=follow-up; hr=hours; min=minutes; Q2W=every 2 weeks.

[a] Every other dose (Day 3 of Dose 8, 10, 12, etc., regardless if TSR-033 is administered alone or in combination with dostarlimab).

[b] End of infusion of the last investigational drug, ie, on days when TSR-033 is administered alone, the draw is post end of TSR-033 infusion (Dose 2, Dose 3, Dose 5, Dose 6, et), and when TSR-033 is given in combination with dostarlimab, the draw should be taken at the end of the dostarlimab infusion (Dose 1, Dose 4, etc). The end of infusion PK sample should always be drawn at the end of the last study medication infusion, regardless if the infusion is slowed or temporarily stopped due to an infusion reaction.

[c] For ADA sample collection. This sample collection time will coincide with the safety follow up visits.

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

Table 17: Sampling Schedule for Biomarkers and Biopsies: Part 1a, 1b, 1c, and Part 2A

Visit/Dose: / Day: / Procedure (Protocol Section):	Screening	Dose 1		Dose 2	Dose 3	Dose 5	Dose 7	Dose 10	EOT[a]
		Day 1	Day 8	Day 1	Day 1	Day 1	Day 1	Day 1	
CCI [redacted]									
Fresh tumor tissue biopsies (Section 6.6.2)	X				X[c]				X
Archival tumor tissue (required for Part 1; recommended, if available for Part 2A) (Section 3.3.1.1)	X								

Abbreviations: EOT=end of treatment; PD=progressive disease.

[a] The EOT visit should occur within 7 days of the decision to discontinue study treatment for any reason. Samples will be obtained only for patients who discontinue study treatment due to PD.

[b] The on-study ctDNA sample should be obtained 4 to 6 weeks following Dose 1 (between Dose 3-4).

[c] The on-study biopsy should be obtained 4 to 6 weeks following Dose 1 (between Dose 3-4).

Table 18: Sampling Schedule for Biomarkers and Biopsies: Part 2B (Cohorts B1 and B2)

Visit/Dose:	Screening	Dose 1		Dose 2	Dose 3	Dose 5	Dose 7	Dose 10	EOT[a]
Day:		Day 3	Day 10	Day 3	Day 3	Day 3	Day 3	Day 3	
Procedure (Protocol Section):									
CCI									
Fresh tumor tissue biopsies (Section 6.6.2)	X				X[c]				X
Archival tumor tissue (recommended, if available) (Section 3.3.1.1)	X								

Abbreviations: EOT=end of treatment; PD=progressive disease.

[a] The EOT visit should occur within 7 days of the decision to discontinue study treatment for any reason. Samples will be obtained only for patients who discontinue study treatment due to PD.

[b] The on-study ctDNA sample should be obtained 4 to 6 weeks following Dose 1 (between Dose 3-4).

[c] The on-study biopsy should be obtained 4 to 6 weeks following Dose 1 (between Dose 3-4).

8. STATISTICAL METHODS

All descriptive statistical analyses will be performed using the most recently released and available SAS statistical software, unless otherwise noted. For categorical variables, the number and percent of each category within a parameter will be calculated. For continuous variables, the sample size (n), mean, median, and standard deviation, as well as the minimum and maximum values, will be presented. Missing data will not be imputed unless otherwise stated. There will be a detailed description of patient disposition; patient demographics and baseline characteristics will be summarized.

No formal interim analysis is planned for this study. However, a review of safety data and available preliminary PK data will be conducted by the Sponsor and Investigators following completion of the DLT observation periods in Part 1a and Part 1c. Determination of the RP2D will be based on review of safety, PK, and CCI [redacted]. All analyses will be performed for any patient that received any amount of study drug. All analyses for efficacy will use Dose 1, Day 1 as the start time.

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

Analysis populations will be defined as follows for Part 1 and Part 2, respectively:

- Safety Population: All patients who receive any amount of study drug.
- Efficacy Population: All patients who receive any amount of TSR-033.
- DLT Evaluable Population: The assessment of DLTs in Part 1a, Part 1c, and Part 2B will include only those patients completing the DLT observation period throughout the course of 2 TSR-033 administrations (ie, Day 1 and Day 15 in the first 28 days of study treatment) for Part 1a, the course of 2 TSR-033 + dostarlimab administrations (ie, Day 1 and Day 21 in the first 42 days of study treatment) for Part 1c, the course of 2 TSR-033 + dostarlimab administrations (ie, Day 3 and Day 17 in the first 30 days of study treatment) unless the patient discontinued TSR-033 (Part 1a) or TSR-033 + dostarlimab (Part 1c and Part 2B) due to a DLT.
- Per Protocol Population: All patients in the Efficacy Population who do not have protocol violations during the study that may significantly impact the interpretation of efficacy results and have ≥1 post-baseline disease assessment.
- PK Population: All patients who receive any amount of TSR-033 and/or dostarlimab and have ≥1 measurable drug concentration. PK Populations will be defined separately for each study drug.
- Immunogenicity (ADA) Population: All patients who receive any amount of TSR-033 and have ≥1 ADA sample with a result.

Demographics, baseline characteristics, and medical history information will be summarized by dose level for Parts 1a, 1b, and 1c and by expansion cohorts for Part 2, for the Safety Population using descriptive statistics. No formal statistical comparisons among cohorts will be performed.

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

8.2. Safety Analyses

The following key safety parameters will be evaluated by dose level, by expansion cohorts, and overall, unless noted otherwise:

- DLTs (DLT-Evaluable Population) during the DLT-observation period in Part 1a, Part 1c, and Part 2B.
- Incidence of TEAEs during the DLT-observation period (ie, the first 28 days of treatment for Part 1a and the first 42 days of treatment for Part 1c) compared to subsequent days with subsequent doses.
- Incidence of TEAEs, irAEs, and SAEs occurring while patients are on treatment or up to 90 days after the last dose of study drug or until alternative anti-cancer therapy is initiated, whichever occurs first.
- Clinical laboratory assessments (CBC with 5-part differential, chemistry, and thyroid panel), CTCAE graded laboratory toxicities, ECOG PS, ECG parameters, and usage of concomitant medications.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system and displayed in tables and data listings using system organ class and preferred term. Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined per protocol as any AE with onset after the first administration of study drug, throughout the treatment period, until 90 days after cessation of study treatment (or until the start of alternative anti-cancer 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. DLTs will be tabulated by dose level in Part 1a, Part 1c, and Part 2B.

The number and percentage of patients with any TEAE, with any TEAE assessed by the Investigator as related to treatment (definite, probable, or possible relationship), and with any SAE will be summarized by treatment group and overall. In these tabulations, each patient will contribute only once (ie, 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 will also be provided for the following: patient deaths, SAEs, and AEs leading to withdrawal of study treatment.

8.2.1. Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary (September 2016 or later version). A dictionary listing of all unique concomitant medications used in the study will be provided.

8.3. Pharmacokinetic Analyses

All patients who receive any amount of TSR-033 and/or dostarlimab and have ≥1 measurable drug concentration will be included in PK analyses.

Noncompartmental methods will be used to evaluate the PK characteristics of TSR-033 in Part 1a and Part 1b and TSR-033 and dostarlimab in Part 1c and Part 2, as appropriate. PK parameters such as C_{max}, time at maximum concentration (T_{max}), AUC, $t_{½}$, volume of distribution at steady state (V_{ss}), and clearance (CL) may be derived from serum concentrations using actual sampling times, as data permit. Concentration data may be included in a population PK analysis, the results of which will be reported separately.

Concentration-time data and PK parameters will be listed and summarized descriptively by cohort, dose level, and dose number. Summary statistics will include the mean, standard deviation, coefficient of variation, geometric mean, geometric mean coefficient of variation, median, minimum, and maximum.

8.4. Antidrug Antibody Analysis

The number and percent of patients who become positive for ADAs will be summarized by visit/time and overall. Similar analysis may be conducted for neutralizing antibodies (NAbs) if deemed appropriate.

8.5. Efficacy Analyses

All efficacy endpoints will be summarized on the data from patients in Part 2 by expansion cohort; in addition, data may be pooled for patients in Part 1 and Part 2, by tumor type. The primary efficacy analysis is based on the Efficacy Population defined in Section 8.1. 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. Time-to-event analyses will be performed using Kaplan-Meier (KM) methods.[22] Comparisons in the Part 1 portion of the study will be made using descriptive statistics.

8.5.1. Primary Efficacy Parameter

The primary efficacy endpoint will be ORR for Part 2A of the study, defined as the achievement of CR or PR using RECIST v1.1, as assessed by the Investigator. Point estimates and 2-sided 95% CIs will be provided. The primary analysis of ORR will be performed for each expansion cohort and no multiplicity adjustment will be made since separate inferences will be drawn for each cohort.

8.5.2. Secondary Efficacy Parameters

ORR is a secondary endpoint for Part 1 and Part 2B of the study, defined as the achievement of CR or PR using RECIST v1.1, as assessed by the Investigator.

DCR is a secondary endpoint for Part 2 and is defined as the proportion of patients achieving CR, PR, or SD as assessed by the Investigator per RECIST v1.1, with point estimates and 2-sided 95% CIs. SD per RECIST v1.1 for a minimum of 12 weeks is necessary for inclusion in evaluation of DCR.

DOR is a secondary endpoint for Part 2 and 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.

CCI [redacted]

8.7. Determination of Sample Size

Ascending doses of TSR-033 in Part 1a and in combination with dostarlimab in Part 1c will be evaluated to identify the respective RP2Ds. The actual number of patients accrued during this phase will be determined largely by the safety and PK findings observed during the course of their treatment. RP2D decisions for Part 1a and Part 1c will be based on a minimum of 6 patients for each regimen. Patients in Part 1b (PK/PDy cohort) will not be considered evaluable for dose escalation purposes (ie, not included into the DLT-evaluable population), but will contribute to the overall safety assessment at the dose level being evaluated. It is expected that up to approximately 132 patients will be enrolled in Part 1 as follows:

Part 1a (TSR-033 monotherapy dose escalation): Approximately 30-54 patients

*Part 1b (TSR-033 monotherapy PK/*CCI [redacted]*:* Approximately 18-30 patients

Part 1c (TSR-033 + dostarlimab combination dose escalation): Approximately 24-48 patients

A total of up to approximately 55 patients are anticipated in the 2 planned expansion cohorts in Part 2.

Part 2A (TSR-033 + dostarlimab combination dose expansion in anti-PD-1-naïve third- or fourth-line MSS-CRC patients): A null hypothesis of ORR 10% will be tested against an alternative hypothesis of ORR 25%. The trial is designed using a one-sided exact test that achieves a minimum of 80% power at alpha level of 0.1. A sample size of 31 will provide an attained power of 82.4% and an attained type-1 error of 0.083. The null hypothesis will be rejected if 6 or more responses are observed in the 31 patients.

Part 2B (TSR-033 + dostarlimab combination given with mFOLFOX6 or FOLFIRI and bevacizumab [SOC] in anti-PD-1-naïve second-line MSS-CRC patients): A null hypothesis of ORR 20% will be tested against an alternative hypothesis of ORR 40%. The trial is designed using a one-sided exact test that achieves a minimum of 80% power at alpha level of 0.1. A sample size of 24 will provide an attained power of 80.8% and an attained type-1 error of 0.089. The null hypothesis will be rejected if 8 or more responses are observed in the 24 patients.

9. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

9.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to TESARO, Inc. before he/she can enroll any patient/subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. TESARO, Inc. will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

9.2. 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 Site 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.

9.3. Institutional Review Board

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval and all materials approved by the IRB for this study, including the patient consent form and recruitment materials, must be maintained by the Investigator and made available for inspection.

9.4. 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.

9.5. 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. Trial subject's medical files should be retained for at least 5 years (recommended to be in their original format) and in accordance with the maximum period of time permitted by the hospital, institution, or private practice. If the Investigator becomes unable to respond for their essential documents (eg, relocation, retirement), the Sponsor should be notified of this change and informed as to whom the responsibility has been transferred.

9.6. Good Clinical Practice

This study will be conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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).

9.7. 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; 1 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 in the medical record.

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.

9.8. 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 US, following approval, the protocol amendment(s) will be submitted to the Investigational New Drug Application 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.

9.9. 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 not be identified on study documents by name, but rather by their enrollment number or birth date, or in accordance with local regulations. Documents that identify the patient (eg, the signed ICF) must be maintained in confidence by the Investigator.

9.10. 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).

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

9.11. 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.

9.12. 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, IB, ICF, 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.

9.13. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for TESARO, Inc. or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

9.14. Study Termination

If the Sponsor, an Investigator, or Clinical Monitor discovers conditions arising during the study that indicate that the clinical development of an investigational product should be placed on hold due to an unacceptable patient risk, then TESARO, Inc. will determine whether the study must be terminated after appropriate consultation with the Investigators. In addition, TESARO, Inc. may independently decide at any time to suspend or discontinue development of the investigational product.

Within 15 days of premature closure, TESARO Inc. must notify the competent authorities and IECs of any member state where the study is being conducted, providing the reasons for study closure.

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APPENDIX 1. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (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 1 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 nonpathological in size (<10 mm short axis).

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

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) or maintenance of tumor marker level, or both, above the normal limits.

Progressive Disease (PD): Appearance of 1 or more new lesions or unequivocal progression of existing non-target lesions, or both. 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 the 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 19: RECIST Response for Patients with Measurable Disease (ie, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response When Confirmation is Required[a]
CR	CR	No	CR	>4 weeks. Confirmation[b]
CR	Non-CR/Non-PD	No	PR	>4 weeks. Confirmation[b]
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 weeks from baseline[b]
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD[c]	Yes or No	PD	
Any	Any	Yes	PD	

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.
[a] See RECIST v1.1 publication for further details on what is evidence of a new lesion.
[b] Only for nonrandomized trials with response as primary endpoint.[53]
[c] In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease 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 20: RECIST Response for Patients with Nonmeasurable Disease

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

Abbreviations: CR=complete response; PD=progressive disease.
Note: A "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.


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APPENDIX 3. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Description	ECOG Grade[55]
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, ie, 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

APPENDIX 4. COCKCROFT-GAULT FORMULA

A commonly used equation for calculating an estimate of CrCL, 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[56]

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