CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1b Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of GS-3583, a FLT3 Agonist Fc Fusion Protein, as Monotherapy and in Combination With Anticancer Therapies in Subjects With Advanced Solid Tumors
Short Title:	Study to Assess the Effects of GS-3583 in Participants With Advanced Solid Tumors
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	145581
EudraCT Number:	2022-000927-19
Clinical Trials.gov Identifier:	NCT04747470
Indication:	Advanced Solid Tumors
Protocol ID:	GS-US-496-5657
Contact Information:	The medical monitor's name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 21 October 2020 Amendment 1: 17 March 2022 Amendment 2: 14 April 2022

This study will be conducted under United States Food and Drug Administration investigational new drug (IND) regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area, the United Kingdom, and Switzerland are not included under the IND and are considered non-IND sites.

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation (ICH), Good Clinical Practice (GCP), and applicable regulatory requirements.

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PROTOCOL SYNOPSIS

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IND Number:	145581
EudraCT Number:	2022-000927-19
Clinical Trials.gov Identifier:	NCT04747470
Study Centers Planned:	Approximately 30 centers overall in the United States, European Union, and Asia-Pacific.
Objectives:	**Part 1:** **The primary objectives of Part 1 are as follows:** • To characterize the safety and tolerability of GS-3583 as monotherapy in subjects with advanced solid tumors • To determine the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of GS-3583 as monotherapy in subjects with advanced solid tumors **The secondary objectives of Part 1 are as follows:** • To characterize the pharmacokinetics (PK) of GS-3583 in subjects with advanced solid tumors • To evaluate the immunogenicity of GS-3583 in subjects with advanced solid tumors

The exploratory objectives of Part 1 are as follows:

Part 2:

The primary objective of Part 2 is as follows:

- To assess the safety and tolerability and to determine the RP2D of GS-3583 in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-fluorouracil (5-FU) chemotherapy in subjects with head and neck squamous cell carcinoma (HNSCC) (Cohort A) or in combination with docetaxel in subjects with non-small cell lung cancer (NSCLC) (Cohort B)

The secondary objectives of Part 2 are as follows:

- To evaluate the investigator-assessed confirmed objective response rate (ORR) with GS-3583 in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in subjects with HNSCC (Cohort A) or in combination with docetaxel in subjects with NSCLC (Cohort B)
- To assess the preliminary efficacy of GS-3583 in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy versus zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy alone in subjects with HNSCC (Cohort A) or in combination with docetaxel versus docetaxel alone in subjects with NSCLC (Cohort B) as determined by progression free survival (PFS), duration of response (DOR), and overall survival (OS)

- To evaluate investigator-assessed disease control rate (DCR) with GS-3583 in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in subjects with HNSCC (Cohort A) or in combination with docetaxel in subjects with NSCLC (Cohort B)
- To evaluate the PK of GS-3583 administrated in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in subjects with HNSCC (Cohort A) or in combination with docetaxel in subjects with NSCLC (Cohort B)
- To evaluate the immunogenicity of GS-3583 administrated in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in subjects with HNSCC (Cohort A) or in combination with docetaxel in subjects with NSCLC (Cohort B)

The exploratory objectives of Part 2 are as follows:

Study Design:

Part 1:

Part 1 is a Phase 1b, open-label, multicenter, sequential dose-escalation study to evaluate the safety, tolerability, PK, and preliminary efficacy of GS-3583 in subjects with advanced solid tumors.

Dose Escalation

Subjects with advanced solid tumors will be enrolled in a standard 3 + 3 dose escalation study design to evaluate the safety, tolerability, PK, pharmacodynamics, and to determine the MTD or RP2D level of GS-3583 as monotherapy.

GS-3583 will be administered on Days 1 and 15 of Cycle 1 and on Day 1 of each subsequent 4-week/28-day cycle for up to 13 cycles or until the subject meets study treatment discontinuation criteria. The starting dose is 675 μg and may be modified if the results of the Phase 1a healthy volunteer (HV) study (Study GS-US-496-5619) are available prior to the initiation of this study. Approximately 33 subjects will be enrolled at up to 5 dose levels sequentially. The MTD will be a dose level with acceptable safety and tolerability. The RP2D will be a dose level with acceptable safety, tolerability, PK, and biomarker activities.

In Part 1, the dose-limiting toxicity (DLT) evaluation period is 28 days in Cycle 1 and will start with the initial dose of GS-3583. A subject who fails to receive all GS-3583 treatments or fails to complete all safety assessments in the DLT period for reasons other than DLT will be replaced. The dose-escalation/stay/de-escalation decision will be made by the safety review team (SRT).

Dose escalation to the next cohort will occur if no subjects experience DLTs during the DLT evaluation period. If 1 subject within the initial cohort of 3 subjects experiences a DLT, an additional 3 subjects will be enrolled at the same dose level. If no DLTs are observed in the additional 3 subjects, dose escalation will occur. If ≥ 2 subjects experience DLTs at a dose level, dose de-escalation to a lower dose will occur. The MTD is the highest dose level with a subject incidence of DLTs of < 33% in 6 or more subjects during the first 28 days of study drug dosing. A minimum of 6 subjects need to be treated at a dose level before this dose level can be deemed as the MTD.

Subjects who tolerate GS-3583 beyond the DLT evaluation period will have the option to receive stereotactic body radiation therapy (SBRT) starting at Cycle 2 per investigator's discretion. Provision of SBRT will be according to the institution's own protocol and in line with the local standard of care.

CCI [redacted]

Part 2:

Part 2 is a Phase 1b, open-label, multicenter study evaluating GS-3583 in combination with other anticancer therapies. There will be 2 cohorts in Part 2, each comprising safety run-in and open-label randomized expansion phases. Once the SRT reviews each safety run-in cohort and the sponsor determines the RP2D for that cohort, randomized expansion cohorts will be enrolled.

- Cohort A will enroll subjects with metastatic or unresectable, locally recurrent HNSCC regardless of programmed cell death ligand 1 (PD-L1) status who have not received previous systemic treatment for metastatic disease. In the Safety Run-In Cohort and Treatment Arm of the Randomized Expansion Cohort, GS-3583 will be given in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy. Subjects in the Control Arm will receive zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy.
- Cohort B will enroll subjects with locally advanced, unresectable or metastatic NSCLC with documented progression on at least one anti–programmed cell death protein 1 (PD-1) or anti-PD-L1 monoclonal antibody (mAb) and platinum-based chemotherapy given individually or in combination. In the Safety Run-In Cohort and Treatment Arm of the Randomized Expansion Cohort, GS-3583 will be given in combination with docetaxel. Subjects in the Control Arm will receive docetaxel alone.

Number of Subjects Planned:	Approximately 150 subjects will be enrolled in total: Part 1: 24 subjects Part 2 Safety Run-in Cohorts A and B: 12 to 36 subjects Part 2 Randomized Expansion Cohort A: approximately 45 subjects (randomized 2:1) Part 2 Randomized Expansion Cohort B: approximately 45 subjects (randomized 2:1)

Target Population:	**Part 1:** Adult subjects aged ≥ 18 years with a histologically or cytologically confirmed locally advanced or metastatic malignant solid tumor that is refractory to or intolerant of standard therapy or for which no standard therapy is available. **Part 2 Cohort A:** Adult subjects aged ≥ 18 years with a histologically or cytologically confirmed diagnosis of metastatic HNSCC who have not previously received systemic therapy for metastatic disease or with recurrent disease who were considered incurable by local therapies. **Part 2 Cohort B:** Adult subjects aged ≥ 18 years with a histologically or cytologically confirmed locally advanced or metastatic NSCLC with documented progression on at least one anti-PD-1 or anti-PD-L1 mAb and platinum-based chemotherapy given individually or in combination.
Duration of Treatment:	**Part 1:** GS-3583 will be administrated for a maximum of 13 cycles or until unacceptable toxicity, progressive disease, or other reasons for discontinuation listed in the protocol. **Part 2:** GS-3583 will be administered for a maximum of 8 cycles as follows: • In Cohort A (HNSCC), subjects will receive GS-3583 for an additional 2 cycles after the completion of chemotherapy. This will amount to a maximum of 8 cycles of GS-3583 since there will be a maximum of 6 cycles of chemotherapy. Should the chemotherapy be terminated prior to Cycle 6 (due to reasons other than disease progression), GS-3583 will be continued for an additional 2 cycles. • In Cohort B (NSCLC), docetaxel will be given until 1 or more criteria for discontinuation are met; and not limited by number of cycles. For these subjects, GS-3583 will be given for a maximum of 8 cycles. Should docetaxel be terminated prior to Cycle 6 (due to reasons other than disease progression), GS-3583 will be continued for an additional 2 cycles.

In Part 2, subjects who prematurely discontinue GS-3583 may be able to continue other study drugs and remain on the study if they are deemed to continue to derive benefit from those drugs. However, such cases must be discussed with and approved by the medical monitor.

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria:

Subjects must meet all of the following inclusion criteria to be eligible for participation in Part 1 or Part 2 of this study:

1) Voluntarily agree to participate by giving a signed written informed consent
2) Age ≥ 18 years
3) Have measurable disease on imaging based on response evaluation criteria in solid tumors Version 1.1 (RECIST V1.1) (Appendix 7). Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. Historical images within 28 days of the screening visit may be accepted as a screening image if deemed acceptable in the opinion of the investigator.
4) Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 for Part 1 and ECOG of 0-1 for Part 2
5) Diagnosis
    a) **Part 1:** Histologically or cytologically confirmed diagnosis of locally advanced or metastatic malignant solid tumor that is refractory to or intolerant of standard therapy or for which no standard therapy is available
    b) **Part 2 Cohort A (HNSCC):**
        i) Subjects must have histologically or cytologically-confirmed recurrent or metastatic HNSCC that is considered incurable by local therapies.
        ii) Subjects should not have had prior systemic therapy administered in the recurrent or metastatic setting. Systemic therapy which was completed more than 6 months prior to signing consent if given as part of multimodal treatment for locally advanced disease is allowed.
        iii) The eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx.

iv) Subjects with a primary tumor site of nasopharynx (any histology) are not allowed.

v) Subjects must provide adequate tissue for biomarker analysis at baseline (fine needle aspirate [FNA] is not adequate). Repeat samples may be required if adequate tissue is not provided. This specimen may be the diagnostic sample for subjects with a new diagnosis of metastatic HNSCC. If obtained for a subject with recurrent disease for locally advanced disease, then it must be obtained after completion of the previous initial management with no other treatment from the time of biopsy until the start of study treatment. Subjects must also have a combined positive score (CPS) at baseline using a locally available, validated test.

Note: In Randomized Expansion Cohort A, no more than 10 subjects with CPS < 1 will be enrolled in the Treatment Arm and no more than 5 subjects with CPS < 1 will be enrolled in the Control Arm.

vi) Subjects must have results from local testing of HPV for oropharyngeal cancer defined as p16 IHC testing using a locally available validated test.

Note: Subjects with oral cavity, hypopharynx, or larynx cancer are not required to undergo HPV testing by p16 IHC as by convention they are assumed to be HPV negative.

c) Part 2 Cohort B (NSCLC):

i) Subjects must have histologically or cytologically confirmed locally advanced, unresectable or metastatic NSCLC with documented progression on at least 1 anti-PD-1 or anti-PD-L1 mAb and platinum-based chemotherapy. Anti-PD-1 or anti-PD-L1 mAb and platinum-based chemotherapy may have been given individually or in combination.

ii) Includes subjects who received prior platinum-based chemoradiotherapy (with or without maintenance anti-PD-L1 antibody) for Stage 3 disease. To be considered to have progressed during or after prior treatment with platinum-based chemotherapy, subjects should have either received prior platinum-based chemotherapy in the recurrent or metastatic setting or have experienced disease

progression within 6 months of last dose of platinum-based chemotherapy administered as part of concurrent chemoradiation for Stage 3 disease or as neoadjuvant or adjuvant therapy. To be considered to have progressed during or after prior treatment with an anti-PD-1 or anti-PD-L1 antibody, subjects should have either received this therapy in the recurrent or metastatic setting or have experienced disease progression during "maintenance" treatment following concurrent chemoradiation for Stage 3 disease.

These subjects must be tested for epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS1, and PD-L1. Testing for other actionable genomic alterations is recommended and to be performed as per local standard of care.

iii) Subjects with EGFR, ALK, ROS1, or any other known actionable genomic alterations must have also received treatment with at least 1 approved therapy appropriate to the genomic alteration, unless these options are not available to the subjects.

1) **Note:** No additional treatments are allowed in the recurrent/metastatic setting for subjects with no actionable genomic alterations.

iv) Documented radiographic disease progression while on or after receiving the most recent treatment regimen for advanced or metastatic NSCLC.

v) Subjects with mixed small-cell lung cancer and NSCLC histology are not eligible.

vi) Subjects must provide adequate tissue for biomarker analysis at baseline (FNA is not adequate). Repeat samples may be required if adequate tissue is not provided. It must be obtained after completion of the previous line of therapy with no other treatment from the time of biopsy until the start of study treatment.

6) Life expectancy of ≥ 3 months, in the opinion of the investigator

7) Adequate organ function as assessed by hematological, renal, and hepatic parameters and no clinically significant coagulopathy as indicated by the following laboratory values (Hematologic laboratory values must be met at screening visit and maintained without transfusional or growth factor support within 2 weeks of study drug initiation):

System	Laboratory Value[a]
Hematological[b]	
Absolute Neutrophil Count (ANC)	≥ 1.5×10^9/L
Platelets[c]	**Part 1 and Part 2 Cohort B (NSCLC):** ≥ 100×10^9/L **Part 2 Cohort A (HNSCC):** ≥ 75×10^9/L
Hemoglobin[c]	**Part 1:** ≥ 8 g/dL (≥ 9.5 g/dL in subjects with cardiac disease) **Part 2:** ≥ 9 g/dL (≥ 9.5 g/dL in subjects with cardiac disease)
Renal	
Creatinine Clearance[c]	**Part 1 and Part 2 Cohort B (NSCLC):** ≥ 50 mL/min by the Cockcroft-Gault method **Part 2 Cohort A (HNSCC):** ≥ 60 mL/min by the Cockcroft-Gault method
Hepatic	
Total Bilirubin	≤ 1.5 × ULN
AST (SGOT) and ALT (SGPT)[c]	**Part 1 and Part 2 Cohort A (HNSCC):** ≤ 3 × ULN (≤ 5 × ULN in subjects with liver metastases) **Part 2 Cohort B (NSCLC):** ≤ 2.5 × ULN (≤ 5 × ULN in subjects with liver metastases)
Serum albumin[c]	**Part 2 Cohort B (NSCLC) only:** > 3 g/dL
Coagulation[d]	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤ 1.5 × ULN unless the subject is receiving anticoagulant therapy
Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 × ULN unless the subject is receiving anticoagulant therapy

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal

a All screening laboratory tests must be reviewed by the investigator and be acceptable prior to enrollment.

b Hematologic laboratory values must be met at screening visit and maintained without transfusional or growth factor support within 2 weeks of study drug initiation.
c Adequate laboratory values differ by study part and/or cohort due to differences in anti-cancer agents used in Part 2.
d Subjects on full-dose oral anticoagulation, must be on a stable dose (minimum duration 14 days prior to the screening visit). Subjects on low molecular weight heparin will be allowed. In subjects receiving warfarin, the recommended INR is ≤ 3.0 with no active bleeding (ie, no bleeding within 14 days prior to first dose of study drug).

8) A negative serum pregnancy test is required for female subjects (unless permanently sterile or greater than 2 years postmenopausal as described in Appendix 5).

9) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception and refrain from egg or sperm donation as described in Appendix 5.

10) All acute toxic effects of prior antitumor therapy resolved to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Grade ≤ 1 before the first dose of study drug, with the exception of Grade 2 alopecia and peripheral neuropathy.

11) Lactating females must agree to discontinue nursing before the study drug is administered until 12 weeks after the last dose of study drug.

12) Able and willing to comply with the protocol requirements

Exclusion Criteria:

General Exclusion Criteria:

Subjects who meet *any* of the following exclusion criteria are not eligible to be enrolled in Part 1 or Part 2 of this study:

1) Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 3 weeks of the first dose of treatment

2) Has received prior systemic cytotoxic chemotherapy, biological therapy, radiotherapy, or major surgery within 3 weeks of Cycle 1 Day 1; a 1-week washout is permitted for palliative radiation to non-central nervous system (CNS) disease with medical monitor approval

3) Is expected to require any other form of systemic or localized anticancer therapy while on study (including maintenance therapy with another agent, and/or surgical resection); for subjects enrolled in Part 1 of the study, provision of SBRT per local standard of care is acceptable beyond the DLT evaluation period starting at Cycle 2. Hormonal/endocrine therapy for prostate cancer or breast cancer is permitted.

4) Has known severe hypersensitivity reactions (NCI CTCAE Grade ≥ 3) to fully human mAbs or fusion proteins, GS-3583 formulation excipients, or severe reaction to immuno-oncology agents, such as colitis or pneumonitis requiring treatment with corticosteroids, any history of anaphylaxis, or uncontrolled asthma

5) Is receiving systemic corticosteroid therapy 1 week prior to the first dose of study treatment or receiving any other form of systemic immunosuppressive medication

   Note: The following corticosteroid uses are permitted: use as premedication for known hypersensitivity reactions (eg, IV contrast, IV drug infusions); intraocular, intranasal, inhaled, and/or topical corticosteroids; and/or prednisone at doses of up to 10 mg per day or equivalent. The use of physiologic doses of corticosteroids may be approved after consultation with the medical monitor.

6) Has concurrent active malignancy other than nonmelanoma skin cancer, carcinoma in situ of the cervix, or superficial bladder cancer who has undergone potentially curative therapy with no evidence of disease. Subjects with other previous malignancies are eligible if disease free for > 2 years.

7) Previous history of hematological malignancy, MGUS or other preleukemic states (Presence of CHIP/ ARCH is acceptable)

8) Has a known CNS metastasis(es), unless metastases are treated and stable and the subject does not require systemic corticosteroids for management of CNS symptoms at least 1 week prior to study treatment. Subjects with history of carcinomatous meningitis are excluded regardless of clinical stability.

9) Has active autoimmune disease that requires systemic treatment (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs)

   Note: Subjects with diabetes type 1, vitiligo, psoriasis, hypothyroid disease, or hyperthyroid disease, not requiring immunosuppressive treatment are eligible.

10) Has had an allogeneic tissue/solid organ transplant

11) Has evidence of active pneumonitis

12) Has a serious systemic fungal, bacterial, viral, or other infection that is not controlled or requires IV antibiotics

13) Previously known or existing FLT3 mutation of any kind

14) Has known active HBV and/or HCV, and/or HIV

    a) Subjects must be negative for hepatitis B surface antigen and total anti-HBc. For subjects where total anti-HBc-positive, HBV DNA by quantitative polymerase chain reaction will be required.

    b) Subjects must be negative for HCV antibody. For subjects with positive HCV antibody, HCV RNA by quantitative polymerase chain reaction will be required.

    c) Subjects must also be negative for HIV at screening

15) Subjects with cardiovascular disease/abnormalities will be excluded per the following criteria:

    a) Has clinically significant (ie, active) cardiovascular disease: cerebral vascular accident/stroke or myocardial infarction within 6 months of enrollment, unstable angina, congestive heart failure (New York Heart Association class III or IV), or serious uncontrolled cardiac arrhythmia requiring medication

    b) Has systolic dysfunction defined as ejection fraction < 45% measured by echocardiogram (ECHO) (or multigated acquisition [MUGA] scan). Results from ECHO or MUGA scan performed up to 30 days prior to enrollment are acceptable.

16) History or evidence of clinically significant disorder, condition, laboratory abnormality, or disease that, in the opinion of the investigator or medical monitor would pose a risk to subject safety or interfere with the study evaluations, procedures, or completion

17) Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study

18) Is legally incapacitated or has limited legal capacity

19) Uncontrolled intercurrent illness or significant illnesses during the screening period

20) Part 2 Cohort A HNSCC

    a) Has disease that is suitable for local therapy administered with curative intent.

    b) Has progressive disease (PD) within 6 months of completion of curatively-intended systemic treatment for locoregionally advanced HNSCC

21) Part 2 Cohort B NSCLC

    a) Previously received treatment with docetaxel as monotherapy or in combination with other agents

    b) NSCLC that is eligible for definitive local therapy alone

22) Have received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu and COVID-19 vaccines that do not contain live virus are permitted.

Study Procedures/ Frequency:

Screening:

Screening will commence with obtaining the subject's signed informed consent and will occur up to 28 days prior to the first dose of study drug.

Screening procedures will include the following: medical history and baseline symptoms review, full physical exam (PE), vital signs, 12-lead electrocardiogram (ECG), ECHO (or MUGA scan), Eastern Cooperative Oncology Group (ECOG) performance status, prior/concomitant medication review, blood collection for pregnancy test (females of child bearing potential), chemistry, hematology, coagulation, endocrine function, HIV, HBV, and HCV, urinalysis, adverse event (AE) assessment, whole blood samples for CHIP mutation analysis and analysis of circulating tumor DNA, CCI [redacted] and computed tomography (CT) or magnetic resonance imaging (MRI) (scans that meet protocol requirements that are obtained as part of standard medical practice up to 28 days prior to the baseline visit [Cycle 1 Day 1] are acceptable). Subjects in Part 2 Cohort A (HNSCC) only will have baseline

CPS and HPV testing (for those with cancer of oropharynx) performed by p16 immunohistochemistry (IHC) using a locally available validated assay. Subjects in Part 2 Cohort B (NSCLC) only will have baseline information on EGFR, ALK, ROS1, or any other known actionable genomic alterations. Subjects in Part 2 Randomized Expansion Cohorts shall undergo a mandatory tumor biopsy if the investigator considers that no undue risk is posed to the subjects due to biopsy related procedures; a fresh baseline biopsy is preferred, but a recent archival tumor biopsy obtained after the end of the last line of therapy and not older than 6 months may be substituted.

Treatment:

In Part 1, subjects will receive GS-3583 on Days 1 and 15 of Cycle 1 and on Day 1 of each subsequent 4-week/28-day cycle; up to a maximum of 13 cycles.

In Part 2, subjects will receive GS-3583 on Day 1 of each 3-week/21-day cycle up to a maximum of 8 cycles.

Safety and efficacy assessments will occur on an outpatient basis, including assessment of tumor response, PE, vital signs, ECG, ECOG performance status, collection of blood samples (for routine safety labs, GS-3583 PK, immunogenicity, pharmacodynamic markers, and other biomarkers at applicable visits), stool samples, urine pregnancy test (at least every 4 weeks while receiving GS-3583 in females of childbearing potential), and assessment of AEs.

Subjects will undergo CT/MRI scans every 8 weeks during Part 1 of the study or every 6 weeks during Part 2 of the study. A subject who does not show evidence of disease progression by clinical assessment or by CT/MRI or other applicable scan may continue receiving GS-3583 for the maximum of cycles (52 weeks [13 cycles] in Part 1 and 24 weeks [8 cycles] in Part 2) or until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other protocol-specified reasons for treatment discontinuation.

Posttreatment:

After discontinuation of all study treatment, all subjects will be followed for safety for 60 days.

Following discontinuation of GS-3583, subjects who do not present with progressive disease and/or start a new anticancer therapy will continue tumor imaging assessments every 8 weeks (in Part 1) and every 6 weeks (± 7 days) from the first treatment dose until Week 24, then every 9 weeks thereafter starting at Week 33 (in Part 2) until documented progressive disease, initiation of a new anticancer therapy, or up to 1 year after the last dose of study drug, whichever occurs first. Thereafter, these subjects will move into survival follow-up and will be contacted via telephone call every 3 months for up to a year after the completion/discontinuation of tumor lesion assessments to report development of any new malignancies other than that which was being studied during treatment with GS-3583.

For subjects who permanently discontinue from the study in the absence of progressive disease/or start of a new line of anticancer therapy and will not be continuing tumor imaging during the posttreatment period, additional imaging is recommended at the EOT visit if the last imaging was performed more than 30 days prior.

Pharmacokinetic Assessments

Part 1:

At Cycles 1 and 3, blood will be collected at predose (≤ 30 minutes before start of infusion), end of infusion (+ 5 minutes), and 2 hours (± 10 minutes), 6 hours (± 0.5 hours), Day 2 (24 hours [± 2 hours]), Day 3 (48 hours [± 4 hours]), Day 5 (96 hours [± 4 hours]), Day 8 (168 hours [± 12 hours]), Day 15 (for Cycle 1: pre-Day 15 dose [≤ 30 minutes before start of infusion], end of Day 15 infusion [+ 5 minutes), and 2 hours after start of Day 15 infusion [± 10 minutes]; for Cycle 3: 336 hours [± 12 hours]), and Day 24 (552 hours [± 12 hours]) after start of the Day 1 infusion

In addition, samples will be collected on Day 1 (predose) and Day 15 (336 hours) of Cycles 2, 4, and every subsequent even numbered cycle thereafter, and at the 60-day follow-up visit (approximately 60 days after last dose). An additional blood sample will be collected at the EOT visit if a subject terminates early from study treatment.

Serum concentrations of GS-3583 will be determined, and PK parameters will be estimated.

Part 2:

GS-3583 (Safety Run-in Cohorts): At Cycles 1 and 3, blood samples will be collected at predose (≤ 30 minutes before start of infusion), end of infusion (+ 5 minutes), and 2 hours (± 10 minutes), 6 hours (± 0.5 hours), Day 8 (168 hours [± 12 hours]), and Day 15 (336 hours [± 12 hours]) after start of the Day 1 infusion.

In addition, blood samples will be collected on Day 1 (predose [≤ 30 minutes before start of infusion] and end of infusion [+ 5 minutes]) of Cycles 2, 5, and every subsequent odd numbered cycle thereafter, and at the 60-day follow-up visit (approximately 60 days after last dose). An additional blood sample will be collected at the EOT visit if a subject terminates early from study treatment.

GS-3583 (Randomized Expansion Cohorts Treatment Arms): Blood samples will be collected on Day 1 (predose [≤ 30 minutes before start of infusion] and end of infusion [+ 5 minutes]) of Cycles 1, 2, 3, and every subsequent odd numbered cycle thereafter, and at the 60-day follow-up visit (approximately 60 days after last dose). An additional blood sample will be collected at the EOT visit if a subject terminates early from study treatment.

Part 2 Cohort A:

Zimberelimab (Safety Run-in Cohort and Randomized Expansion Cohort Control and Treatment Arms): Blood samples will be collected on Day 1 (predose [≤ 30 minutes before start of infusion] and end of infusion [+ 5 minutes]) of Cycles 1, 2, 3, and every subsequent odd numbered cycle thereafter, and at the 60-day follow-up visit (approximately 60 days after last dose). An additional blood sample will be collected at the EOT visit if a subject terminates early from study treatment.

Biomarker Assessments

Part 1:

Whole blood biomarker samples will be collected and peripheral blood mononuclear cells (PBMCs) and plasma will be isolated to measure pharmacodynamic biomarkers for GS-3583 at the following time points relative to the start of infusion:

Day 1 of Cycle 1 and Cycle 3 at predose, Day 8 (168 hours), Day 15 (336 hours, must be collected predose at Cycle 1), and Day 24 (552 hours) after start of the Day 1 infusion. The predose samples will be collected any time prior to the start of infusion at the Day 1 visit. However, for Cycle 1 Day 1 an additional set of predose samples should be collected up to 72 hours prior to the Cycle 1 Day 1 visit, if feasible.

In addition, samples will be collected at predose on Day 1 and Day 15 (336 hours) of Cycles 2, 4, and every subsequent even numbered cycle thereafter, and at the 60-day follow-up visit (approximately 60 days after last dose). An additional sample will be collected at the EOT visit if a subject terminates early from study treatment.

A separate whole blood sample to determine blood cell counts will be drawn at the same time points as the above pharmacodynamic samples.

Additional biomarker samples will be collected per protocol Section 6.5.2.

Pharmacodynamic biomarkers will include, but are not limited to, analysis of dendritic cells (DCs) (type 1 and type 2 conventional dendritic cells [cDC1s and cDC2s]) and plasmacytoid DCs, monocytes and CD135 (FMS-related tyrosine kinase 3).

Part 2:

Safety Run-in Cohorts:

Whole blood biomarker samples will be collected and PBMCs and plasma will be isolated to measure pharmacodynamic biomarkers for GS-3583 at the following time points relative to the start of infusion:

Predose at Day 1, and on Day 12 (264 hours [± 12 hours]), and Day 15 (336 hours [± 12 hours]) after start of the Day 1 infusion of Cycles 1 and 3. In Cycle 1 and Cycle 3, the predose samples will be collected any time prior to the start of infusion at the Day 1 visit. However, for Cycle 1 Day 1, additional set of predose samples should be collected up to 72 hours prior to the Cycle 1 Day 1 visit, if feasible.

In addition, samples will be collected at predose on Day 1 and Day 15 (336 hours) of Cycles 2, 4, and every subsequent even numbered cycle thereafter, and at the 60-day follow-up visit (approximately 60 days after last dose). An additional sample will be collected at the EOT visit if a subject terminates early from study treatment.

A separate whole blood sample to determine blood cell counts will be drawn at the same time points as the above pharmacodynamic samples.

Additional biomarker samples will be collected per protocol Section 6.5.2.

Pharmacodynamic biomarkers will include, but are not limited to, analysis of dendritic cells (DCs) (type 1 and type 2 conventional dendritic cells [cDC1s and cDC2s]) and plasmacytoid DCs, monocytes and CD135 (FMS-related tyrosine kinase 3).

Randomized Expansion Cohorts:

Whole blood biomarker samples will be collected and PBMCs and plasma will be isolated to measure pharmacodynamic biomarkers for GS-3583 at the following time points relative to the start of infusion:

Predose on Day 1 and on Day 15 (336 hours [± 12 hours]) after start of the Day 1 infusion of Cycles 1, 2, 3, 4, and every subsequent even numbered cycle thereafter. However, for Cycle 1 Day 1, an additional set of predose samples should be collected up to 72 hours prior to the Cycle 1 Day 1 visit, if feasible.

In addition, samples will be collected at the 60-day follow-up visit (approximately 60 days after last dose). An additional sample will be collected at the EOT visit if a subject terminates early from study treatment.

A separate whole blood sample to determine blood cell counts will be drawn at the same time points as the above pharmacodynamic samples.

Additional biomarker samples will be collected per protocol Section 6.5.2.

Pharmacodynamic biomarkers will include, but are not limited to, analysis of dendritic cells (DCs) (type 1 and type 2 conventional dendritic cells [cDC1s and cDC2s]) and plasmacytoid DCs, monocytes and CD135 (FMS-related tyrosine kinase 3).

	Immunogenicity Assessments **Part 1:** Serum samples will be collected for immunogenicity assessments of GS-3583 at predose (≤ 30 minutes before start of infusion) on Day 1 of Cycles 1, 2, 3, 4, 7, and 13; and at the 60-day follow-up visit (approximately 60 days after last dose). An additional blood sample will be collected at the EOT visit, if a subject terminates early from study treatment. **Part 2 (Safety Run-in Cohorts and Randomized Expansion Cohorts Treatment Arms):** Subjects will have antidrug antibody (ADA) assessed at predose (≤ 30 minutes before start of infusion) on Day 1 of Cycle 1, 2, 3, 5, 9 and 17; and at 60-day follow-up visit (approximately 60 days after last dose). An additional blood sample will be collected at the EOT visit if a subject terminates early from study treatment. **Part 2: Cohort A:** Zimberelimab: **Subjects will have ADA assessed at predose (≤ 30 minutes before start of infusion) on Day 1 of Cycle 1, 2, 3, 5, 9, and 17; and at 60-day follow-up visit (60 days after last dose). An additional blood sample will be collected at the EOT visit if a subject terminates early from study treatment.**
Test Product, Dose, and Mode of Administration:	**Part 1:** On Days 1 and 15 of Cycle 1 and on Day 1 of each subsequent 4-week/28-day cycle, GS-3583 will be given as an IV infusion over 60 (± 10) minutes. The dose and the dosing frequency will be: Cohort 1: Up to 675 μg (Dose Level 1) every 2 weeks for the first 3 doses; subsequent doses will be given every 4 weeks Cohort 2: Up to 2000 μg (Dose Level 2) every 2 weeks for the first 3 doses; subsequent doses will be given every 4 weeks Cohort 3: Up to 6000 μg (Dose Level 3) every 2 weeks for the first 3 doses; subsequent doses will be given every 4 weeks Cohort 4: Up to 12,000 μg (Dose Level 4) every 2 weeks for the first 3 doses; subsequent doses will be given every 4 weeks Cohort 5: Up to 20,000 μg (Dose Level 5) every 2 weeks for the first 3 doses; subsequent doses will be given every 4 weeks

	The dose levels and number of cohorts may be adjusted based on the available PK and pharmacodynamic data from the Phase 1a HV study (GS-US-496-5619). **Part 2 Safety Run-In Cohorts and Randomized Expansion Cohorts, Treatment Arms:** The recommended GS-3583 dose for Part 2 will be determined based on the safety, PK, pharmacodynamics, and all other relevant data from Part 1 and will not exceed the MTD in Part 1. **Part 2 Cohort A:** Zimberelimab 360 mg IV infusion over 60 min ± 5 min on Day 1 of each cycle (up to 105 weeks) Platinum (cisplatin or carboplatin): • Cisplatin 100 mg/m² of body surface area (BSA) IV infusion over 1 hour (or infusion duration per local practice) on Day 1 of each cycle (up to 6 cycles) or • Carboplatin AUC of 5 mg/mL/min IV infusion over 1 hour (or infusion duration per local practice) on Day 1 of each cycle (up to 6 cycles) 5-FU 1000 mg/m^2 of BSA/day continuous IV infusion over 96 hours on Day 1 to Day 4 of each cycle (up to 6 cycles) **Part 2 Cohort B:** Docetaxel 75 mg/m^2 of BSA IV infusion over 60 min ± 10 min on Day 1 of each cycle (until 1 or more discontinuation criteria are met)
Reference Therapy, Dose, and Mode of Administration:	**Part 2 Randomized Expansion Cohort A, Control Arm:** Zimberelimab 360 mg IV infusion over 60 min ± 5 min on Day 1 of each cycle (up to 105 weeks) Platinum (cisplatin or carboplatin): • Cisplatin 100 mg/m² of body surface area (BSA) IV infusion over 1 hour (or infusion duration per local practice) on Day 1 of each cycle (up to 6 cycles) or

	• Carboplatin AUC of 5 mg/mL/min IV infusion over 1 hour (or infusion duration per local practice) on Day 1 of each cycle (up to 6 cycles) 5-FU 1000 mg/m^2 of BSA/day continuous IV infusion over 96 hours on Day 1 to Day 4 of each cycle (up to 6 cycles) **Part 2 Randomized Expansion Cohort B, Control Arm:** Docetaxel 75 mg/m2 of BSA IV infusion over 60 min ± 10 min on Day 1 of each cycle (until 1 or more discontinuation criteria are met)
Criteria for Evaluation:	
Safety:	Safety will be evaluated by assessment of clinical laboratory tests, physical examination, 12-lead ECG, vital signs measurements, ECOG performance status, and the documentation of AEs. AEs will be graded using NCI CTCAE v5.0.
Efficacy:	Efficacy will be evaluated according to RECIST V1.1. In Part 1, imaging will be performed every 8 weeks. In Part 2, imaging will be performed every 6 weeks until Week 24, then every 9 weeks thereafter. Efficacy will be evaluated by ORR (complete response [CR] + partial response [PR], assessed as per RECIST V1.1), and PFS, defined as the interval from first dosing date of study drug to the earlier of the first documentation of definitive disease progression or death from any cause.
Pharmacokinetics:	Serum drug concentrations will be analyzed. The PK parameters to be estimated and reported may include, but may not be limited to, C_{max}, AUC_{tau}, C_{trough}, T_{max} and CL.
Pharmacodynamics:	Pharmacodynamics will be evaluated by monitoring longitudinal changes in the absolute number of DCs (cDC1s and cDC2s) and plasmacytoid DCs, monocytes, and CD135 expression level on these cells, pretreatment and posttreatment.

Statistical Methods:	Analysis sets are defined in Section 8.3.1. Safety Analysis DLTs will be summarized by dose level for subjects in the DLT analysis set. Safety data will be summarized by dose level and/or treatment for subject in the Safety Analysis Set. In general, categorical and ordinal data will be summarized by count and percentage of subjects. Continuous data will be summarized by descriptive summary statistics (mean, standard deviation, minimum, quartiles, median, and maximum). Efficacy Analysis Efficacy data will be summarized by treatment and/or tumor types, as appropriate, for subjects in the Full Analysis Set. Efficacy endpoints will include but may not be limited to ORR, DCR, PFS, DOR, and OS. Subjects who do not have sufficient baseline or on-study tumor assessments to characterize response will be counted as non-responders. Response rate and the corresponding 90% CIs based on the Clopper-Pearson exact method will be provided. Time to event endpoints such as PFS will be analyzed using Kaplan-Meier (KM) method. Pharmacokinetic Analysis GS-3583 or zimberelimab serum concentrations and PK parameters will be described and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variations, standard deviation, median, minimum, and maximum) by dose level/cohort for subjects in the PK Analysis Set. Sample Size For Part 1, assuming up to 4 planned dose levels will be tested with up to 3 DLT-evaluable subjects for the first dose level and up to 6 DLT-evaluable subjects per subsequent dose level, 21 DLT-evaluable subjects will be needed. Assuming 10% are not evaluable, approximately 24 subjects will be enrolled in Part 1. For Part 2, a maximum of 63 subjects will be enrolled for each cohort. Six to 18 subjects will be evaluated in Safety Run-In Cohorts, and 45 subjects will be enrolled in Randomization Expansion Cohorts with 2:1 randomization ratio. The total maximum sample size in Part 2 is approximately 126.

This study will be conducted in accordance with the guidelines of Good Clinical Practice including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	antidrug antibody
AE	adverse event
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	antibody against hepatitis B core antigen
ARCH	age-related clonal hematopoiesis
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_{tau}	area under the concentration versus time curve over the dosing interval
BSA	body surface area
CD	cluster determinant
cDC1	conventional type-1 dendritic cells
cDC2	conventional type-2 dendritic cells
CDDP	cis-diamminedichloroplatinum(II)
CHIP	clonal hematopoiesis of indeterminate potential
CI	confidence interval
CL	clearance
C_{max}	maximum observed concentration of drug
CNS	central nervous system
COVID-19	coronavirus disease 2019
CPS	combined positive score
CR	complete response
CRO	contract/clinical research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	concentration at the end of the dosing interval
CyTOF	cytometry by time-of-flight
DC	dendritic cell
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOT	end of treatment
EU	European Union
EudraCT	European Clinical Trials Database
Fc	fragment crystallizable
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FLT3	FMS-related tyrosine kinase 3
FLT3L	FMS-related tyrosine kinase 3 ligand
FNA	fine needle aspirate
5-FU	5-flourouracil
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
Gilead	Gilead Sciences
GLP	Good Laboratory Practice
GLPS	Gilead Global Patient Safety
GM-CSF	granulocyte macrophage colony-stimulating factor
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
HR	hazard ratio
HV	healthy volunteer
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
Ig	immunoglobulin
IHC	immunohistochemistry
IND	investigational new drug
irAEs	immune related adverse events
IRB	institutional review board
IV	intravenous(ly)
IXRS	interactive voice/web response system

Kd	affinity constant
KM	Kaplan-Meier
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	monoclonal gammopathy of unknown significance
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition (scan)
NCI	National Cancer Institute
NK	natural killer
NCCN	National Comprehensive Cancer Network
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PE	physical exam
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RT	radiotherapy
SAE	serious adverse event
SBRT	stereotactic body radiation therapy
SOP	standard operating procedure
SRT	safety review team
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction

TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
TLR3	toll-like receptor 3
T_{max}	time (observed time point) of C_{max}
TME	tumor microenvironment
TTR	time to response
US	United States
w/v	weight-to-volume ratio

1. INTRODUCTION

1.1. Background

Despite unprecedented clinical activity across multiple types of cancer with programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) blockade therapy, the majority of subjects do not respond (primary resistance) or develop resistance after initial tumor regression (acquired resistance) {Sharma 2017}. This is due, at least in part, to poor T-cell infiltration into the tumor, which is negatively correlated with treatment response {Tumeh 2014}. Therefore, the development of novel approaches to increase T-cell infiltration within the tumor microenvironment (TME) is hypothesized to increase the number of subjects benefiting from immunotherapy. To this point, evidence indicates critical roles for tumor-residing Batf3-dependent conventional type-1 dendritic cells (cDC1s) (migratory CD103+ and lymphoid CD8a+ dendritic cells [DCs] in mice, and CD141+ DCs in humans) in priming and expansion of tumor-specific CD8+ T cells {Hildner 2008, Oba 2020, Roberts 2016} and their recruitment to the TME {Spranger 2017}. Unique among the various DC subsets, cDC1s display enhanced abilities to phagocytose dead cells, and to cross-present exogenous antigens onto major histocompatibility complex (MHC) class I molecules {Shortman 2010}. Although sparse in the TME, cDC1s can be recruited by systemic or intratumoral injection of FMS-like tyrosine kinase 3 ligand (FLT3L) {Hammerich 2019, Hegde 2020}.

FMS-related tyrosine kinase 3 ligand (FLT3L) is a hematopoietic growth factor that binds to FMS-related tyrosine kinase 3 (FLT3) on myeloid and lymphoid progenitor cells in the bone marrow and terminally differentiated DCs {Lyman 1998}. FLT3 activation by FLT3L promotes receptor dimerization and phosphorylation leading to signaling events that promote proliferation and inhibit cell death {Parcells 2006}. Notably, FLT3L-mediated receptor signaling is required for the differentiation, expansion, and maintenance of DCs in peripheral and lymphoid organs. FLT3 or FLT3L-deficient mice have defective hematopoiesis, resulting in a profound reduction in the systemic DC compartment {Durai 2018}.

Dendritic cells are immune cells that effectively link the innate and adaptive arms of the immune system. Dendritic cells present antigens to naive and antigen-experienced (memory) T cells via major histocompatibility complex class I and II to regulate T-cell expansion and differentiation and the acquisition of effector functions {Merad 2013}. Productive antitumor immune responses in nonclinical models depend on a subtype of DCs termed cDC1 {Bottcher 2018}. In the context of cancer, cDC1s are prime tumor-reactive T cells in the regional draining lymph nodes through presentation of tumor-derived antigens {Broz 2014, Zelenay 2012}.

GS-3583 is a fusion protein composed of the extracellular domain of a recombinant human FLT3L fused to an engineered fragment crystallizable (Fc) region of a human immunoglobulin (Ig) G4. GS-3583 is designed to expand cDC1s in tumors and draining lymph nodes. The cDC1s capture and present tumor-derived antigens to T cells via major histocompatibility complex class I and II, leading to their subsequent activation and antitumor effector function. Nonclinical models and clinical trials using recombinant FLT3L (CDX-301, Celldex Therapeutics) have established the therapeutic potential of expanding cDC1s {Borges 1999, Hammerich 2019,

Salmon 2016}. However, the unfavorable pharmacokinetic (PK) properties of the recombinant FLT3L limit the duration of cDC1 expansion and thus its therapeutic potential {Anandasabapathy 2015}. GS-3583 is engineered to demonstrate superior PK properties compared to recombinant FLT3L, allowing for sustained cDC1 expansion in subjects and potential alignment with the dosing schedules for established immunotherapies. Treatment of cancer subjects with GS-3583 is expected to potentiate the activity of standard of care or immunomodulatory intervention therapeutics.

The safety, PK, and pharmacodynamics (as assessed by DC expansion) of multiple ascending doses of recombinant FLT3L (CDX-301) given subcutaneously for up to 10 days has previously been investigated in healthy volunteers (HVs) {Anandasabapathy 2015}. Overall, recombinant FLT3L was well tolerated. Likewise, GS-3583 was investigated in a first-in-human (FIH) study in HVs to evaluate the safety, tolerability, PK, and pharmacodynamics. Escalating single doses ranging from 75 µg to 2000 µg of GS-3583 were well tolerated and there were no serious or Grade 3 or higher adverse events (AEs) {Rajakumaraswamy 2021}.

Whereas mobilization of cDC1s alone is insufficient in generating antitumor T-cell responses in established tumors, systemic or intratumoral administration of a toll-like receptor 3 (TLR3) agonists as well as CD40 agonists activate cDC1s and enhances responses to anti-PD-1/PD-L1 therapy {Salmon 2016, Sanchez-Paulete 2016}. Radiotherapy (RT) has been shown to cause immunogenic death of cancer cells, which can trigger DC activation, antigen presentation, and priming of tumor-specific CD8+ T cells {Demaria 2016}, and can be employed for enhancing FLT3L-induced cDC1 function in the tumor. Indeed, there is nonclinical and clinical data from T-cell-inflamed tumors showing that in situ vaccination with FLT3L, RT, and TLR3 agonist facilitates cross-priming of tumor-specific T cells, and synergizes with PD-1 blockade {Hammerich 2019}. Nonetheless, the vast majority of subjects with cancer do not present with tumor sites and/or lesions that are amenable to radiation which renders it a suboptimal mode for activating cDC1s. On the other hand, certain chemotherapeutic agents have the potential to trigger immunogenic death of cancer cells although their potential to activate the cDC1s expanded by FLT3L has not previously been investigated.

The current study, GS-US-496-5657, is designed to investigate the safety, tolerability, and preliminary efficacy of GS-3583 as monotherapy (Part 1) and in combination with other anticancer therapies (Part 2).

Part 1 of the study will investigate GS-3583 given intravenously (IV) as monotherapy to subjects with advanced solid tumors in dose-escalation cohorts in order to determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) as monotherapy.

Part 2 of the study will investigate GS-3583 in combination with other anticancer therapies. There will be 2 cohorts in Part 2:

- Cohort A will consist of subjects with metastatic or unresectable, locally recurrent head and neck squamous cell carcinoma (HNSCC) who have not received previous systemic treatment for metastatic disease. GS-3583 will be combined with zimberelimab and platinum (cisplatin or carboplatin) + 5-fluorouracil (5-FU) chemotherapy.

- Cohort B will consist of subjects with locally advanced, unresectable or metastatic non–small-cell lung cancer (NSCLC) with documented progression on at least one anti-PD-1 or anti-PD-L1 monoclonal antibody (mAb) and platinum-based chemotherapy given individually or in combination. For these subjects, GS-3583 will be given in combination with docetaxel.

Part 2 of the study will test the hypothesis that the induction and activation of tumor-residing cDC1s will facilitate the priming, expansion, and infiltration of tumor-specific CD8+ T cells into the poorly T-cell inflamed TME, and improve responsiveness to anti-PD-L1 therapy (in HNSCC) and chemotherapy (in NSCLC). It is hypothesized that systemic administration of GS-3583 (FLT3L Fc fusion protein) will result in the mobilization of cDC1s to the TME whereas systemic administration of chemotherapy will induce immunogenic death of cancer cells, resulting in the maturation and activation of antigen-loaded cDC1s for priming and expansion of tumor-specific CD8+ T cells.

1.1.1. HNSCC

Head and neck squamous cell carcinoma (HNSCC) is diagnosed in over 550,000 patients per year globally and is responsible for over 380,000 deaths {Global Burden of Disease Liver Cancer Collaboration 2017}.

According to the Global Burden of Disease study, lip and oral cavity cancers are the 15th most common cancers worldwide and are in the top 10 in South and Southeast Asia, Tropical Latin America, and Sub-Saharan Africa. The incidence has increased by 36.5% in the past decade {Global Burden of Disease Liver Cancer Collaboration 2017, Siegel 2017, Simard 2014}. Laryngeal cancers are the 20th most common and have increased by 23.1% in the past 10 years and other pharynx cancers are the 24th most common and have increased by 29.9% {Global Burden of Disease Liver Cancer Collaboration 2017, Siegel 2017, Simard 2014}.

In the United States (US), head and neck cancers account for approximately 4% of all cancers. The annual incidence in the US is approximately 60,000 new cases, with approximately 14,000 deaths. Throughout all of the anatomical subtypes, males are more likely to be diagnosed with HNSCC than females at a 2:1 to 4:1 ratio {Bray 2008, Lambert 2011}. In some global regions, including areas of France, Hong Kong, India, Central and Eastern Europe, Spain, Italy, and Brazil, the incidence of HNSCC in males is over 20 per 100,000 people {Bray 2008, Lambert 2011}. In the USA, the incidence of laryngeal cancer is 50% higher in African American men compared with the rest of the population {DeSantis 2013}.

Several risk factors are associated with the incidence of head and neck cancers, including tobacco and alcohol consumption. In addition, human papillomavirus (HPV) infection is a causative agent for head and neck cancers. Squamous cell carcinomas account for over 90% of head and neck cancers arising in the oral cavity and larynx. Initial treatment of HNSCC is broken down by extent of disease (localized, locoregionally advanced, and metastatic). Subjects with localized disease (Stage I or II) have a 5-year overall survival (OS) of 70% to 90% and are treated with definitive surgery and/or radiation therapy. In contrast, subjects with metastatic disease have a poor prognosis, with a 5-year OS of approximately 4% {Beckham 2019}.

Systemic therapy with either chemotherapy and/or immune checkpoint inhibition is the standard of care for subjects with recurrent or metastatic disease in the frontline setting.

Recently, immune checkpoint inhibitors, specifically anti-PD-1 antibodies, have been approved for subjects with metastatic HNSCC. Notably, pembrolizumab was recently granted approval for the first-line treatment of metastatic or unresectable, recurrent HNSCC, as a monotherapy in subjects whose tumors express PD-L1 (combined positive score [CPS] ≥ 1) and in combination with 5-FU and platinum chemotherapy in subjects regardless of PD-L1 status. This approval was based on results from a Phase 3, randomized, open-label, active-controlled, multicenter study comparing pembrolizumab monotherapy, pembrolizumab + 5-FU + platinum, and cetuximab + 5-FU + platinum (KEYNOTE-048). In the subgroup of subjects with a PD-L1 CPS ≥ 1, treatment with pembrolizumab monotherapy resulted in an improved median OS compared with cetuximab + 5-FU + platinum (12.3 months versus 10.3 months, respectively; hazard ratio [HR] = 0.78; p = 0.0086) {Burtness 2019}. In the overall study population, regardless of PD-L1 status, treatment with pembrolizumab + 5-FU + platinum resulted in an improved median OS compared with cetuximab + 5-FU + platinum (13.0 months versus 10.7 months, respectively; HR = 0.77; p = 0.0034). Based on these results, pembrolizumab monotherapy for subjects whose tumors express PD-L1 and pembrolizumab + 5-FU + platinum for subjects regardless of PD-L1 status have become standard-of-care options. However, novel agents that can improve OS in both groups are needed to enhance clinical benefit in this population that represents a high unmet medical need.

1.1.2. NSCLC

Lung cancer is the leading cause of cancer-related mortality worldwide. It was estimated that in 2020, there were over 2 million new cases of lung cancer and approximately 1.8 million deaths worldwide {International Agency for Research on Cancer (IARC) 2020}. In the US in 2021, it is estimated that there will be over 235,000 new cases of lung cancer and over 131,000 deaths {American Cancer Society 2021}. Approximately 80% to 85% of all lung cancers are NSCLC {Ettinger 2019} and more than half of these are identified at an advanced stage {Siegel 2019}.

Immune checkpoint inhibitor therapy has dramatically improved the prognosis of advanced lung cancer. Immune checkpoint inhibitor therapies, as monotherapy (PD-1 ≥ 50%) or in combination with platinum doublet chemotherapy (regardless of PD-L1 expression), are mainly used in the frontline metastatic setting based on results of Studies KN-024, KN-042, KN-189, and KN-407 and similar studies for subjects who do not have actionable genomic alterations {KEYTRUDA 2021}. Platinum doublet chemotherapy with or without PD-L1 inhibitor remains the standard treatment for subjects with actionable genomic alterations when they have failed treatment with targeted agents or such treatment is not available. After failure of immune checkpoint inhibitor therapy and platinum-based chemotherapy, there are limited treatment options for most subjects. According to the current National Comprehensive Cancer Network guidelines, the use of single agent chemotherapy (including taxanes) is the standard of care for subjects with recurrent or metastatic NSCLC after failure of platinum-based therapy and/or immune checkpoint therapy regardless of presence of genomic alterations and PD-L1 status. The main options for single agent chemotherapy in this setting generally include docetaxel (with or without ramucirumab)

and pemetrexed (for nonsquamous tumors, if not previously used). In a study of docetaxel versus best supportive care in relapsed NSCLC, the median progression-free survival (PFS) was approximately 3 months with a median OS of approximately 6 to 8 months {Shepherd 2000}. These numbers have been borne out in more contemporaneous studies with docetaxel following failure of platinum-based regimens in NSCLC {Horn 2017, Mazieres 2021}.

Although docetaxel is considered standard of care in subjects failing platinum-based regimens and checkpoint inhibitors, a significant unmet medical need remains in the treatment of patients who have progressed following anti-PD-1/anti-PD-L1 therapy.

1.2. Background on Study Interventions

1.2.1. GS-3583

1.2.1.1. General Information

GS-3583 is a fusion protein composed of a recombinant human FLT3L extracellular domain fused to an engineered Fc region of a human IgG4. GS-3583 binds to human FLT3 with high affinity and potently activates signaling. GS-3583 has attenuated binding to activating Fc gamma receptors to avoid the depletion of FLT3 expressing progenitor cells and DCs and enhanced binding to the neonatal Fc receptor to increase its in vivo half-life. A murine surrogate of GS-3583 showed single dose antitumor activity in nonclinical tumor models, which correlated with peripheral and intratumoral DC expansion. Based on mechanism of action, GS-3583 has the potential to combine with a range of cancer therapies, including chemotherapy and immune checkpoint blockade.

For further information on GS-3583, refer to the current investigator's brochure (IB), including information on the following:

- Nonclinical PK and in vitro metabolism
- Nonclinical pharmacology and toxicology

1.2.1.2. Nonclinical Pharmacology and Toxicology

1.2.1.2.1. Nonclinical Pharmacology

GS-3583 binds to recombinant human FLT3 with an estimated affinity constant (Kd) of 36 nM. It potently activates FLT3 signaling in cell-based assays, with a half-maximal effective concentration (EC_{50}) of 0.053 nM, and induces expansion of primary human cDC1 in vitro with an EC_{50} of 0.25 nM. GS-3583 showed a dose-dependent and prolonged pharmacodynamic response in the peripheral blood of cynomolgus monkeys, as compared to recombinant FLT3L. In nonclinical tumor models, a murine surrogate of GS-3583 (GS-1062398) exhibited single agent efficacy that correlated with peripheral and intratumoral pharmacodynamic assessments. In addition, GS-1062398 combined effectively with PD-L1 pathway blockade to provide superior efficacy versus single agents alone.

1.2.1.2.2. Nonclinical Toxicology

The cynomolgus monkey was selected as a suitable toxicology species based on a high sequence homology for the human FLT3L (95%) and the human Ig heavy constant gamma region (92%). In single dose and multidose non-Good Laboratory Practice (GLP) PK/pharmacodynamic IV studies in the cynomolgus monkey, GS-3583 was well tolerated up to a 10 mg/kg/dose given once weekly over 2 weeks, and 1000 µg/kg/dose given every 2 weeks over 4 weeks. A high incidence of antidrug antibodies (ADAs), with concurrent loss of systemic exposure, was observed at some of the lower doses, while higher doses (≥ 30 mg/kg once weekly) were not tolerated and necessitated unscheduled euthanasia of some animals.

The nonclinical safety profile of GS-3583 has been characterized in a 4-week GLP IV repeat-dose toxicity study with 4-week recovery period in cynomolgus monkeys. GS-3583 was well tolerated when given IV at doses of up to 10 mg/kg/week for 4 weeks. GS-3583-related findings were noted at all doses and were generally consistent with FLT3 agonism and included the expansion of populations of peripheral monocytes especially, lymphocytes, total white blood cells, neutrophils, and eosinophils to a lesser degree. There was a minimal decrease in red blood cells and associated parameters in females. Immunophenotyping showed a notable expansion of cDC1 and cDC2 cell populations, and serum cytokine changes reflected these cell phenotypes. Also consistent with the pharmacological activity of GS-3583, histiocytic infiltrates detected microscopically in multiple tissues including lymphoid organs. In addition, bone marrow cellularity was increased, consistent with the noted increases in peripheral cell lineages. Enlargement of the spleen and lymph nodes were other findings correlating with the detected microscopic changes. All GS-3583-related findings were considered to be nonadverse. After a 4-week recovery period, there was recovery, or a trend towards recovery in most of the GS-3583-related clinical pathology, gross, and histological changes detected in the terminal groups, although cDC1 and cDC2 subtypes and associated cytokines maintained elevated levels.

1.2.1.3. Clinical Studies of GS-3583

Study GS-US-496-5619 was a Phase 1a, first-in-human, placebo-controlled study of GS-3583 in HVs to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of escalating single doses (ranging from 75 µg to 2000 µg) of GS-3583 {Rajakumaraswamy 2021}. The study was blinded to the subjects and the investigator. Each dose cohort enrolled 8-12 HVs who received GS-3583 or placebo as single IV infusion at 3:1 ratio. Subjects were observed in the Phase-1 unit for 15 days and then for 10 weeks as outpatients. As part of the pharmacodynamic evaluation, the changes in the number of cDC1 and conventional type-2 dendritic cells (cDC2) cells were investigated.

As of 02 July 2021, selected safety, PK, and pharmacodynamic data from all 4 cohorts were available. GS-3583 was well tolerated and all subjects had been discharged. To date, there have been no serious or Grade 3 or higher AEs. Preliminary PK analysis suggested dose-dependent increase in GS-3583 exposure (AUC and C_{max}). Preliminary pharmacodynamic analysis shows that administration of GS-3583 resulted in temporary, dose-dependent increases in cDC1/cDC2 cells that peaked between Days 5 to 11 (higher doses resulted in later peaks) and returned to baseline within 3 weeks of drug administration.

For further information on GS-3583, refer to the current IB.

1.2.2. Information About Combination Therapies

1.2.2.1. Information About Zimberelimab

Zimberelimab is a fully human IgG4 mAb targeting human PD-1. The PD-1 is a type I transmembrane protein that is part of the Ig gene superfamily and the CD28 family of cell surface receptors {Agata 1996}. PD-1 is expressed on T cells and functions as an immune checkpoint that negatively regulates T-cell activation and effector function when activated by its ligands PD-L1 (B7-H1, CD274) and programmed cell death ligand 2 (PD-L2); it plays an important role in tumor evasion from host immunity. Zimberelimab targets, binds to, and inhibits PD-1 and its downstream signaling pathways and hence restoring immune function through the activation of T cells and T-cell-mediated immune responses against tumor cells. Nonclinical data supports its binding to both PD-L1 and PD-L2 and release of the immunosuppressive inhibition of the T-cell effector function after exposure to zimberelimab. Zimberelimab is currently being evaluated for use in cancer patients in both monotherapy and combination studies with approved agents or other experimental regimens. Clinical data from monotherapy treatment in heavily pretreated patients with various advanced solid tumors has established tolerable and pharmacokinetically-stable dosing regimens of zimberelimab IV every 2 and every 3 weeks. Refer to the current zimberelimab IB for clinical studies conducted with zimberelimab.

1.2.2.2. Information About Cisplatin

Cisplatin (cis-diamminedichloroplatinum(II) - CDDP) is an anticancer cytotoxic agent classified as an alkylating agents and is indicated for the treatment of multiple solid tumors, including advanced HNSCC as single agents and in combination with of cytotoxic chemotherapies, targeted agents, and checkpoint inhibitors (CPIs). For current information about cisplatin, refer to the applicable local or regional prescribing information in the pharmacy binder. Any locally available generics for cisplatin may be used.

1.2.2.3. Information About Carboplatin

Carboplatin is a platinum-based chemotherapy drug that is widely used for the treatment of multiple solid tumors, including HNSCC, ovarian, lung, and bladder cancer.

Further information can be found in the current country-specific prescribing information. Any locally available generics for carboplatin may be used.

1.2.2.4. Information About 5-Fluorouracil

5-Fluorouracil is a pyrimidine analog used as a chemotherapy drug and is indicated for the treatment of multiple solid tumors, including colorectal, breast, pancreatic, and gastric adenocarcinoma. It is also used in combination with platinum-based chemotherapy for the treatment of multiple solid tumors, including HNSCC. For current information about 5-FU, refer

to the applicable local or regional prescribing information in the pharmacy binder. Any locally available generics for 5-FU may be used.

1.2.2.5. Docetaxel

Docetaxel is an antineoplastic agent which disrupts the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which inhibits mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use. Docetaxel is indicated for the treatment of multiple solid tumors, including advanced NSCLC, as a single agent. For current information about docetaxel, refer to the applicable local or regional prescribing information in the pharmacy binder. Any locally available generics for docetaxel may be used.

1.3. Rationale for This Study

Despite recent therapeutic improvements in the first-line metastatic HNSCC setting, novel therapies and combinations are needed to extend survival benefit. Recently, the US Food and Drug Administration (FDA) approved pembrolizumab as a monotherapy in subjects whose tumors express PD-L1 (CPS $\geq$ 1) and pembrolizumab in combination with 5-FU and platinum in subjects regardless of PD-L1 tumor expression {KEYTRUDA 2021}. These approvals were based on an approximately 2 to 3-month survival benefit in both settings, demonstrating the need for therapeutic combinations to improve subject benefit. Furthermore, the majority of subjects do not respond (primary resistance) or develop resistance after initial tumor regression (acquired resistance). This may be due, at least in part, to poor T-cell infiltration into the tumor, which is negatively correlated with treatment response. Therefore, the development of novel approaches to increase T-cell infiltration within the TME may increase the number of patients benefiting from immunotherapy. To this point, evidence indicates critical roles for tumor-residing Batf3-dependent cDC1s (migratory CD103+ and lymphoid CD8a+ DCs in mice, and CD141+ DCs in humans) in priming and expansion of tumor-specific CD8+ T cells and their recruitment to the TME. Although sparse in the TME, cDC1s can be recruited by systemic administration of FLT3L {Hammerich 2019, Hegde 2020}. In this study, GS-3583 is utilized to expand and mobilize cDC1s from the hematopoietic progenitors. However, mobilization of cDC1s alone is insufficient to generate antitumor T-cell responses in established tumors–immunostimulation in the form of intratumoral or systemic administration of toll-like receptor 3 (TLR3) agonists, CD40 agonists or radiotherapy, either alone or in combination, is required {Salmon 2016, Sanchez-Paulete 2016}. In the current study, immunogenic chemotherapy from the combination of 5-FU and a platinum agent is hypothesized to provide such immunostimulation to cDC1 cells expanded by GS-3583 which may, in turn, improve the response to immunotherapy.

Similarly, there remains a high unmet need for novel agents in the treatment of advanced NSCLC particularly in subjects who have failed treatment with immune checkpoint inhibitors and platinum-based chemotherapy. Even though much progress has been made in the development of targeted treatments for specific genomic alterations, eventually most subjects have progressive disease on these treatments after which they are treated with platinum chemotherapy with or without immune checkpoint inhibitors. Although docetaxel is considered standard of care in subjects failing platinum-based regimens and checkpoint inhibitors, novel agents remain a significant unmet medical need in subsequent treatment of advanced NSCLC. In a study of docetaxel versus best supportive care in relapsed NSCLC, the median PFS was approximately 3 months with a median OS of approximately 6 to 8 months {Shepherd 2000}. These numbers have been borne out in more contemporaneous studies with docetaxel following failure of platinum-based regimens in NSCLC {Horn 2017, Mazieres 2021}. GS-3583 is hypothesized to improve the antitumor activity seen with docetaxel in NSCLC based on the nonclinical data in syngeneic tumor models (Section 1.3.1). It is postulated that docetaxel induces immunogenic cell death which can trigger the activation and maturation of cDC1s produced by GS-3583, to present antigen, and prime tumor-specific CD8+ T cells in a manner similar to what has been observed with radiotherapy {Demaria 2016, Gupta 2012, Lugade 2005, Weichselbaum 2017}.

Part 1 of this study is designed to assess the safety, tolerability, PK, and preliminary efficacy of GS-3583 given as a monotherapy and determine the MTD. Part 1 will also explore the PK and PK-pharmacodynamic relationship as evaluated by peripheral DC expansion. Once the MTD or RP2D of GS-3583 as monotherapy has been determined, Part 2 of the study will explore GS-3583 in combination with chemotherapy agents with or without a checkpoint inhibitor in NSCLC and HNSCC.

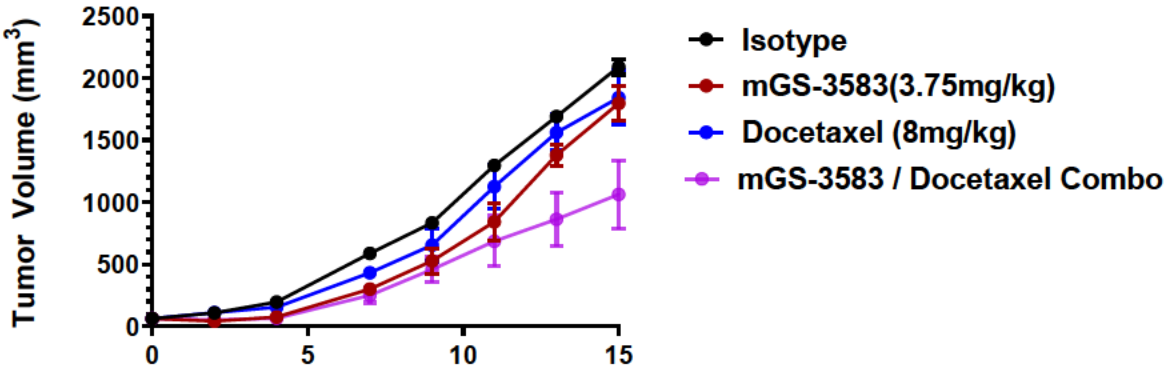
Part 2 of the study utilizes a randomized design in order to assess the contribution of GS-3583 in combination with other anticancer therapies. The randomized design also enables the comparison of the Treatment Arm, which includes GS-3583, with a contemporaneous Control Arm, mitigating the bias associated with historical controls and the need for cross-study comparison.

1.3.1. Rationale for GS-3583 + Chemotherapy Combination

The mouse surrogate GS-1062398 (mGS-3583) was used to assess combination activity with docetaxel in the mouse syngeneic tumor model CT26. Tumor growth inhibition of 50% was achieved with mGS-3583 in combination with docetaxel, as compared to 22% growth inhibition by either mGS-3583 or docetaxel monotherapies, respectively.

The syngeneic mouse colon tumor model, CT26, is not responsive to docetaxel alone and only weakly inhibited by mGS-3583 alone; however, when docetaxel is combined with mGS-3583, the tumor growth is significantly inhibited (Figure 1-1).

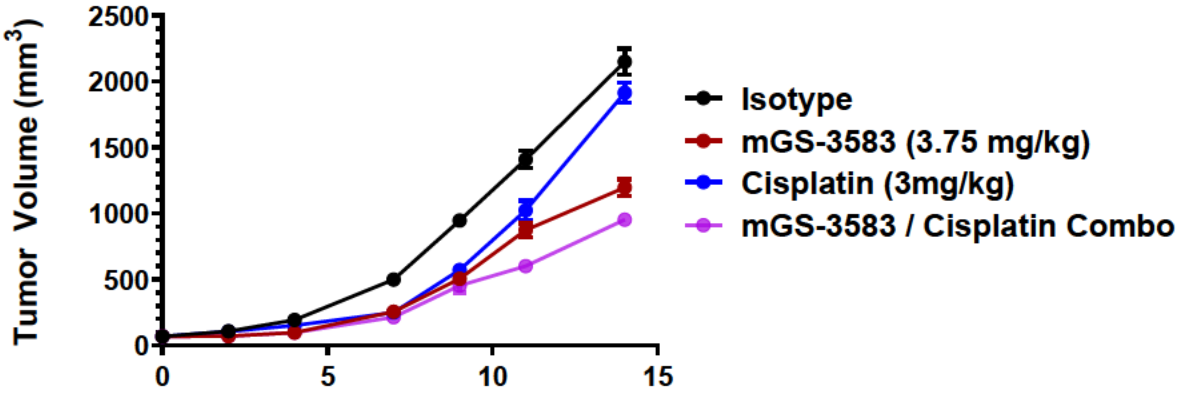
Figure 1-1. **Combination of Murine GS-3583 and Docetaxel Significantly Inhibits Tumor Growth in a Syngenic Murine Colon Carcinoma Cell Line (CT26)**



Cisplatin demonstrated insignificant antitumor efficacy as a monotherapy (tumor growth inhibition [TGI] 11%) in the B16F10 syngeneic tumor model. In contrast, mGS-3583-treated mice showed an average TGI of 45%, which was further enhanced in combination with cisplatin (TGI of 65%). These nonclinical findings support the rationale to assess GS-3583 in combination with chemotherapy.

The murine syngeneic melanoma tumor model, B16F10, is modestly responsive to cisplatin alone or mGS-3583 alone; however, when cisplatin and mGS-3583 are combined, tumor growth is significantly inhibited (Figure 1-2).

Figure 1-2. **Combination of Murine GS-3583 and Cisplatin Significantly Inhibits Tumor Growth in a Syngenic Murine Melanoma Cell Line (B16F10)**

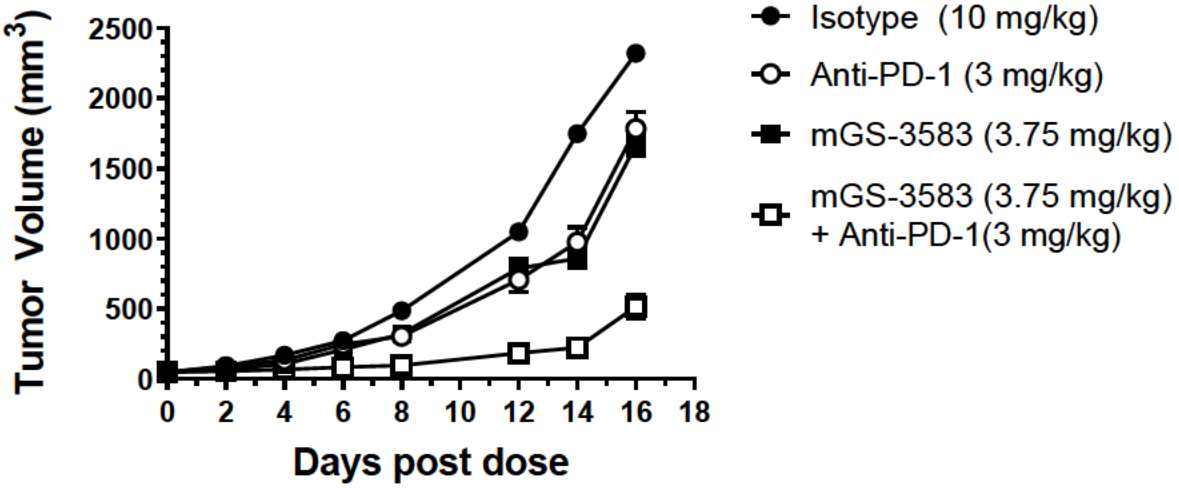


1.3.2. Rationale for GS-3583 + Immunotherapy Combination

The mouse surrogate GS-1062398 (mGS-3583) was used to assess combination activity with PD-1 blockade in 2 syngeneic mouse tumor models. In the MC38 model, TGI of 87% was achieved with mGS-3583 in combination with an anti-PD-1 antibody (GS-878278), as compared to TGI of 51% and 44% by either mGS-3583 or GS-878278 monotherapies, respectively (Figure 1-3). In the B16F10 model, the anti-PD-1 antibody (GS-878278) did not show any significant antitumor efficacy as a monotherapy. By contrast, mGS-3583-treated mice showed an average TGI of 46%, which was further enhanced in combination with GS-878378 (TGI of 64%) (Figure 1-3). These nonclinical findings support the rationale to assess GS-3583 in combination with checkpoint inhibitors targeting the PD-L1 pathway in humans.

The syngeneic mouse tumor model, MC38, is modestly responsive to anti-PD1 blockade or mGS-3583 alone. Together the combination of mGS-3583 with anti-PD-1 blockade elicits significant tumor growth inhibition.

Figure 1-3. Combination of Murine GS-3583 With Anti-PD-1 Blockade Significantly Inhibits Tumor Growth in a Syngenic Murine Colon Carcinoma Cell Line (MC38)



1.4. Rationale for Dose Selection of GS-3583

Selection of the starting dose in Part 1 of this study (675 µg) is supported by the PK/pharmacodynamic assessment of the published CDX-301 data and the exposure-response relationship for GS-3583 in cynomolgus monkeys indicating that the proposed starting dose of GS-3583 is predicted to have negligible biological activity (myeloid DC expansion). The starting dose is further supported by the favorable safety of the recombinant FLT3 ligand, CDX-301, in a Phase 1 multiple-dose, dose-ranging study previously conducted in HVs {Anandasabapathy 2015}. Based on the current PK/pharmacodynamic-guided predictions and the published dose-response data of CDX-301 and the exposure-response relationship for GS-3583 in

cynomolgus monkeys (in terms of cDC1 expansion), GS-3583 doses of 2000 µg may induce cDC1 expansion at therapeutically relevant levels and doses of up to 20,000 µg administered every 4 weeks may help sustain the peak expansion of cDC1 before returning to the baseline. A 4-week dosing interval may be suitable for testing the concept of clinical efficacy in subjects with solid tumors.

The nonclinical safety profile of GS-3583 has been characterized in a 4-week GLP IV repeat-dose toxicity study with 4-week recovery period in cynomolgus monkeys. GS-3583 was well tolerated when given IV at doses of up to 10 mg/kg/week for 4 weeks. The no observed adverse effect level (NOAEL) in the cynomolgus toxicity study was determined to be 10 mg/kg/week, corresponding to an average C_{max} of 385 µg/mL and AUC_{tau} of 40,100 µg•h/mL on Day 22.

On a mg/kg basis, the starting dose of 675 µg GS-3583 in the present study represents a 900-fold safety margin relative to the NOAEL in cynomolgus monkeys. Based on the current PK projections, GS-3583 675 µg multiple doses are predicted to result in C_{max} of 267 ng/mL and AUC_{tau} of 9494 ng•h/mL in humans, which correspond to approximately 1440- and 4224-fold safety margins, respectively, relative to the C_{max} and AUC_{tau} of the 10 mg/kg NOAEL dose in cynomolgus monkeys.

The proposed starting dose, dose levels, and dosing frequency of GS-3583 in Part 1 of the current study (GS-US-496-5657) may be adjusted based on available data from the first-in-human study (GS-US-496-5619) that is currently ongoing in HVs. The first-in-human study is investigating the safety, PK, and pharmacodynamics of single ascending doses of GS-3583 at 75 µg, 225 µg, 675 µg, and 2000 µg. The starting dose of the current study may be adjusted such that any dose level that is found to be well tolerated in HVs will not be repeated.

In Part 1, subjects will receive doses of GS-3583 every 2 weeks for the first 3 doses; all subsequent doses will be given every 4 weeks for a total of up to 52 weeks (13 cycles). In Part 2, subjects will receive GS-3583 every 3 weeks for a total duration of up to 24 weeks (8 cycles). The frequency of dosing is supported by the initial 3 dose levels in Part 1 (in which GS-3583 was administered every 2 weeks) and based on the lack of significant AEs to date (at doses of up to 12,000 µg). The dose level selected for Part 2 safety run-in will not exceed the highest dose level tolerated during Part 1 of the study. Furthermore, Part 2 safety run-in allows the initial evaluation of the safety and tolerability of GS-3583 in combination with other anticancer therapies with the option to dose de-escalate, if required, prior to the enrollment of the Randomized Expansion cohorts.

For further information on GS-3583, refer to the current IB.

1.5. Risk/Benefit Assessment for the Study

The proposed Part 1 of the study aims to evaluate GS-3583 in subjects with advanced malignancies as a single agent to evaluate safety and to determine the MTD/RP2D. Nonclinical investigations provide sufficient evidence that subjects with advanced solid tumors administered GS-3583 would not be exposed to unjustifiable risks.

Based on the nonclinical safety profile of GS-3583, the anticipated risks in subjects will be related to FLT3 agonism and may include expansion of cDC1 and cDC2 cell populations, peripheral monocytes, lymphocytes, total white blood cells, neutrophils, and eosinophils to a lesser degree. There may also be changes in serum cytokine changes that could reflect the change in DC populations; however, this is unlikely to lead to acute release of cytokines or cytokine storm which has not been observed in cynomolgus monkeys, the most sensitive species in the nonclinical toxicology studies.

Part 2 of the study in combination with chemotherapy alone (in NSCLC) or with immunotherapy (in HNSCC) will be started after monotherapy dose escalation is complete and the MTD or RP2D of GS-3583 has been determined. Based on the safety profile observed from the GS-3583 nonclinical studies and the clinical experience to date (both in HVs and subjects with advanced solid tumors), minimal overlapping toxicities are expected between GS-3583 and other combination agents. Nonetheless, to mitigate against any new safety concerns with the proposed combinations, both HNSCC and NSCLC cohorts have a dedicated safety run-in with the option to dose de-escalate GS-3583 prior to further enrollment. It is worth noting that the recombinant FLT3L, CDX-301, has been combined with the immune checkpoint inhibitor pembrolizumab in addition to other immunostimulatory agents in ongoing studies {Hammerich 2019}.

There is postulated risk of developing secondary hematological malignancies with FLT3 activation, based on the observation that aberrant expression of FLT3 is commonly found in hematopoietic malignancies, in particular, acute myeloid leukemia. In most cases, this is due to activating mutations in the FLT3 gene that promote ligand-independent continuous signaling. This theoretical risk has been mitigated by limiting the exposure of subjects to GS-3583 to 12 months in Part 1 of this study, in which subjects have limited life expectancy due to the advanced nature of their malignancies; exposures is further reduced to 24 weeks in Part 2 of the study. Moreover, the related recombinant FLT3L (CDX-301) has safely been administered to more than 500 patients, including over 300 patients for up to 6 months with cancer with no report of secondary leukemia development {Ohri 2018}. There is also theoretical risk of immune related adverse events (irAEs) with agents that modulate the immune system and therefore, any subjects with a history of active autoimmune diseases will be excluded from the study. Some subjects may receive GS-3583 alongside stereotactic body radiation therapy (SBRT) at the discretion of the investigator in line with the local protocol. The recombinant FLT3L (CDX-301) has been administered in combination with SBRT in patients with NSCLC; this combination has been well tolerated.

Subjects may develop ADAs to GS-3583 which may interfere with the physiological actions of endogenous FLT3L. Subjects will be monitored for the development of ADAs and any potential sequalae throughout their treatment period with GS-3583 and at the end of study.

Parameters for discontinuation of study drug are defined in Section 6.10.1.

During a pandemic, additional potential risks to subjects may include adequate study drug availability, interruptions to the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 2 for further details on the risks and risk mitigation strategy.

There may be no direct benefit to subjects participating in this study; however, data from this study will support further development of GS-3583 for the treatment of subjects with advanced solid tumors.

Based on available information, the benefit/risk balance for this study is considered justifiable.

1.6. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

2.1. Objectives: Part 1

The primary objectives of Part 1 are as follows:

- To characterize the safety and tolerability of GS-3583 as monotherapy in subjects with advanced solid tumors
- To determine the MTD or RP2D of GS-3583 as monotherapy in subjects with advanced solid tumors

The secondary objectives of Part 1 are as follows:

- To characterize the PK of GS-3583 in subjects with advanced solid tumors
- To evaluate the immunogenicity of GS-3583 in subjects with advanced solid tumors

The exploratory objectives of Part 1 are as follows:

2.2. Objectives: Part 2

The primary objective of Part 2 is as follows:

- To assess the safety and tolerability and to determine the RP2D of GS-3583 in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in subjects with HNSCC (Cohort A) or in combination with docetaxel in subjects with NSCLC (Cohort B)

The secondary objectives of Part 2 are as follows:

- To evaluate the investigator-assessed confirmed objective response rate (ORR) with GS-3583 in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in subjects with HNSCC (Cohort A) or in combination with docetaxel in subjects with NSCLC (Cohort B)

- To assess the preliminary efficacy of GS-3583 in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy versus zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy alone in subjects with HNSCC (Cohort A) or in combination with docetaxel versus docetaxel alone in subjects with NSCLC (Cohort B) as determined by PFS, duration of response (DOR), and OS

- To evaluate investigator-assessed disease control rate (DCR) with GS-3583 in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in subjects with HNSCC (Cohort A) or in combination with docetaxel in subjects with NSCLC (Cohort B)

- To evaluate the PK of GS-3583 administrated in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in subjects with HNSCC (Cohort A) or in combination with docetaxel in subjects with NSCLC (Cohort B)

- To evaluate the immunogenicity of GS-3583 administrated in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in subjects with HNSCC (Cohort A) or in combination with docetaxel in subjects with NSCLC (Cohort B)

The exploratory objectives of Part 2 are as follows:

3. STUDY DESIGN

3.1. Endpoints

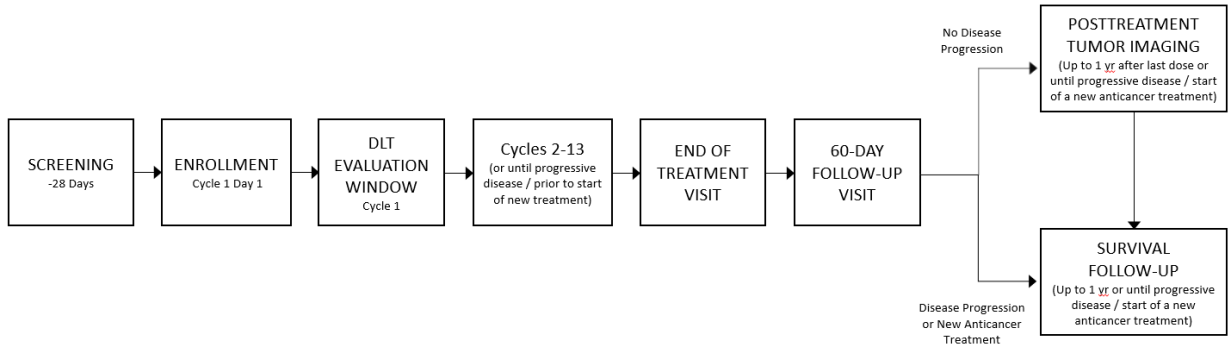
The endpoints of this study are described in Sections 8.1.2 and 8.1.3.

3.2. Study Design

3.2.1. Part 1: Dose Escalation of GS-3583 as Monotherapy

Part 1 is a Phase 1b, open-label study to evaluate the safety, tolerability, PK, and preliminary efficacy of GS-3583 in adult subjects with advanced solid tumors to determine the MTD or RP2D level of GS-3583 as monotherapy. Below is an overview of the study design (Figure 3-1).

Figure 3-1. Part 1 Study Schema



DLT = dose-limiting toxicity

3.2.1.1. Dose Escalation

Subjects with advanced solid tumors who have failed or are intolerant to standard therapy or for whom no standard therapy exists will be sequentially enrolled at progressively higher dose levels to receive GS-3583 as monotherapy.

Dose escalation will proceed using a standard 3 + 3 design as shown in Figure 3-2. The starting dose will be 675 µg and may be modified if the results of the Phase 1a HV study (Study GS-US-496-5619) are available prior to the initiation of this study. Subsequent doses of 2000 µg, 6000 µg, 12,000 µg, and 20,000 µg are planned. Dose level increases will be 3-fold or less (Table 3-1). GS-3583 will be administered on Days 1 and 15 of Cycle 1 and on Day 1 of each subsequent 4-week/28-day cycle for up to 13 cycles or until the subject meets study treatment discontinuation criteria.

Table 3-1. Part 1 Dose Escalation Dose Levels

Dose Level Schema		
Cohort	**GS-3583 (µg)**	**Fold Increase**
1	675	—
2	2000	≤ 3 ×
3	6000	≤ 3 ×
4	12,000	≤ 2 ×
5	20,000	≤ 1.67 ×

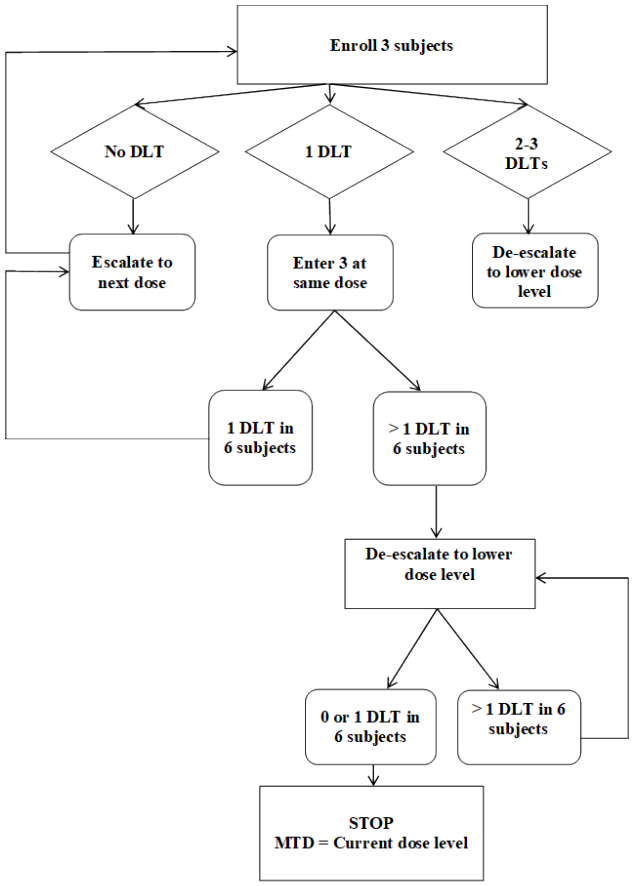
The safety and tolerability of each dose level will be assessed by the safety review team (SRT) after all subjects in the cohort have had 2 doses of GS-3583 and have been followed for at least 28 days after the first dose of GS-3583 or if subjects had dose-limiting toxicities (DLTs) during the first 28 days of study drug dosing.

The initial block of each dose consists of 3 subjects. Dose escalation will occur if no subjects experience a DLT during the first 28 days of study drug dosing. If 1 subject within the initial cohort of 3 subjects experiences a DLT during the first 28 days of study drug dosing, an additional 3 subjects will be enrolled at the same dose level. If no DLTs are observed in the additional 3 subjects, dose escalation will occur. If 2 or more subjects experience DLTs within the first 28 days, dose de-escalation to a lower dose will occur. The MTD is the highest dose level with a subject incidence of DLTs of < 33% in 6 or more subjects during the first 28 days of study drug dosing. A minimum of 6 subjects need to be treated at a dose level before this dose level can be deemed as the MTD. A subject who fails to receive all GS-3583 treatments or fails to complete all safety assessments in the DLT period for reasons other than DLT will be replaced.

The SRT will review safety and relevant clinical data and make the dose-escalation/stay/de-escalation decision. Source data verification is not required to be performed prior to SRT meetings, as there will be alternative quality control checks implemented. These checks will be described in the safety review team charter. The SRT may also add up to 6 additional subjects to any cohort determined to be safe to collect additional safety and PK/pharmacodynamic information. The SRT may also designate intermediate dose levels in addition to the ones listed in Table 3-1 after reviewing all the available safety and PK/pharmacodynamic information.

The dose of GS-3583 taken forward for Part 2 in combination with other anticancer agents will be determined based on all relevant clinical data from all subjects treated in the dose-escalation phase. This dose will not exceed the MTD.

Figure 3-2. 3 + 3 Dose Escalation Scheme



DLT = dose-limiting toxicity; MTD = maximum tolerated dose

3.2.1.1.1. Dose Escalation Criteria

For any given cohort in Part 1, the sponsor may elect to hold dosing, select an intermediate dose, or stop study enrollment at any time based on review of the preliminary safety data.

Based on review of relevant safety and PK data by the SRT, as specified in Section 3.2.3, and in discussion with the investigator, escalation to a higher dose will occur only in the absence of DLTs and/or meeting any prespecified stopping criteria.

3.2.2. DLT Definition

A DLT is any toxicity defined below occurring during the DLT assessment period considered at least possibly related to GS-3583.

- For **Part 1**, the DLT assessment period is from Day 1 through Day 28.
- For **Part 2**, the DLT assessment period is from Day 1 through Day 21.

A DLT may lead to permanent withdrawal of GS-3583 for the subject. The investigator should refer to the American Society of Clinical Oncology (ASCO) Toxicity Management Guidelines (Appendix 3) and withhold or discontinue GS-3583 accordingly.

Hematologic

- Grade ≥ 3 thrombocytopenia with clinically significant bleeding (ie, requires hospitalization, transfusion of blood products, or other urgent medical intervention)
- Grade ≥ 3 febrile neutropenia (absolute neutrophil count [ANC] < 1.0×10^9/L and fever > 101 °F/38.3 °C)
- Any Grade 4 hematologic laboratory abnormalities/AEs regardless of duration will be considered DLTs with the **exception** of:
  - Grade 4 lymphopenia
  - Grade 4 neutropenia lasting ≤ 7 days that is not associated with fever (the use of growth factors is permitted)
  - Grade 4 anemia explained by underlying disease
  - Grade 4 thrombocytopenia lasting ≤ 7 days

Nonhematologic

- Grade ≥ 3 nonhematologic toxicity, except:
  - Transient (≤ 3 days) Grade 3 fatigue, local reactions, headache, nausea, emesis, or diarrhea that are controlled with medical management and/or resolves to Grade ≤ 1 or baseline
  - Any Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
  - Grade 3 AE of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor)
  - Grade 3 rash for ≤ 7 days
  - Transient (≤ 3 days) Grade 3 flu-like symptoms or fever, which are controlled with medical management
  - Transient (≤ 3 days) Grade 3 or higher electrolyte abnormality that is not clinically complicated and resolves spontaneously or responds to conventional medical interventions
  - An event clearly associated with the underlying disease, progressive disease, a concomitant medication, or comorbidity

- Grade ≥ 2 nonhematologic treatment-emergent adverse event (TEAE) that in the opinion of the investigator is of potential clinical significance such that further dose escalation would expose subjects to unacceptable risk

- Any Grade 3 or Grade 4 elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) associated with a Grade 2 elevation in bilirubin lasting ≥ 7 days

- Any irAE for which GS-3583 should be permanently discontinued as described in ASCO Toxicity Management Guidelines (Appendix 3) (eg, any grade encephalitis, Grade ≥ 3 myocarditis, reoccurrence of the same Grade 3 adverse reaction)

Dosing/Procedures-related Toxicities

- **Part 1 only:** Inability to receive the first 2 doses of GS-3583 in Cycle 1 because of related toxicity, even if the toxicity does not meet DLT criteria defined above (regardless of dosing schedule)

Note: Exceptions include DLT exclusions mentioned above.

Grade 5 Event (ie, Death)

3.2.3. Part 2: Disease-specific Cohorts of GS-3583 in Combination With Anticancer Therapies

Part 2 is a Phase 1b, open-label, multicenter study evaluating GS-3583 in combination with other anticancer therapies. There will be 2 cohorts in Part 2, each comprising safety run-in and open-label randomized expansion phases. Each safety run-in cohort will enroll 6 to 18 subjects based on observed toxicities. Once the SRT reviews each safety run-in cohort and the sponsor determines the RP2D for that cohort, randomized expansion cohorts will be enrolled (each randomized expansion cohort may commence enrollment based on the results of the corresponding safety run-in cohort). Up to 45 subjects will be randomized 2:1 to treatment and control arms in each randomized expansion cohort.

- **Cohort A** will enroll subjects with metastatic or unresectable, locally recurrent HNSCC regardless of PD-L1 status who have not received previous systemic treatment for metastatic disease

  — **Safety Run-in Cohort A:** GS-3583 in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy

  — **Randomized Expansion Cohort A:**

    ■ **Treatment Arm:** GS-3583 in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy. No more than 10 subjects with CPS < 1 will be enrolled in this arm.

- **Control Arm:** zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy. No more than 5 subjects with CPS < 1 will be enrolled in this arm.

- **Cohort B** will enroll subjects with locally advanced, unresectable or metastatic NSCLC with documented progression on at least one anti-PD-1 or anti-PD-L1 mAb and platinum-based chemotherapy given individually or in combination.

  - **Safety Run-in Cohort B:** GS-3583 in combination with docetaxel

  - **Randomized Expansion Cohort B:**

    - **Treatment Arm:** GS-3583 in combination with docetaxel

    - **Control Arm:** docetaxel

An overview of the study design for Part 2 is shown in Figure 3-3 and Figure 3-4.

Figure 3-3. Part 2 Study Schema

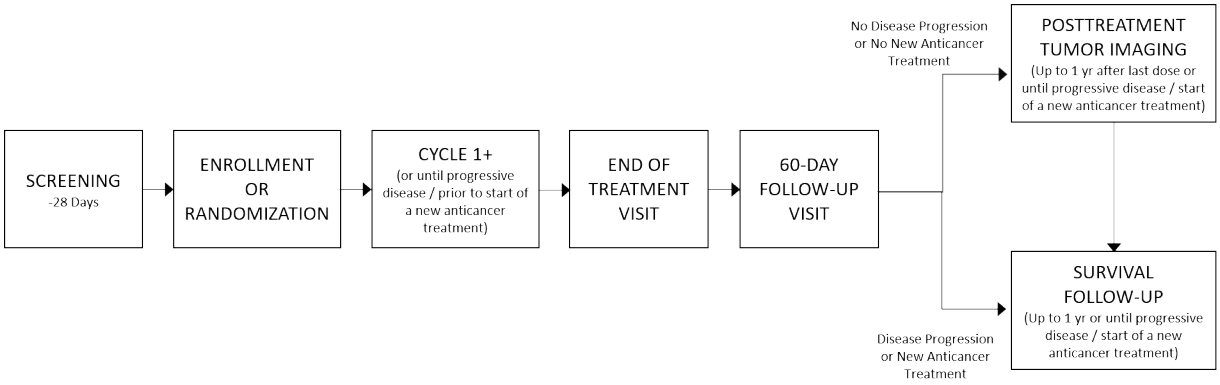
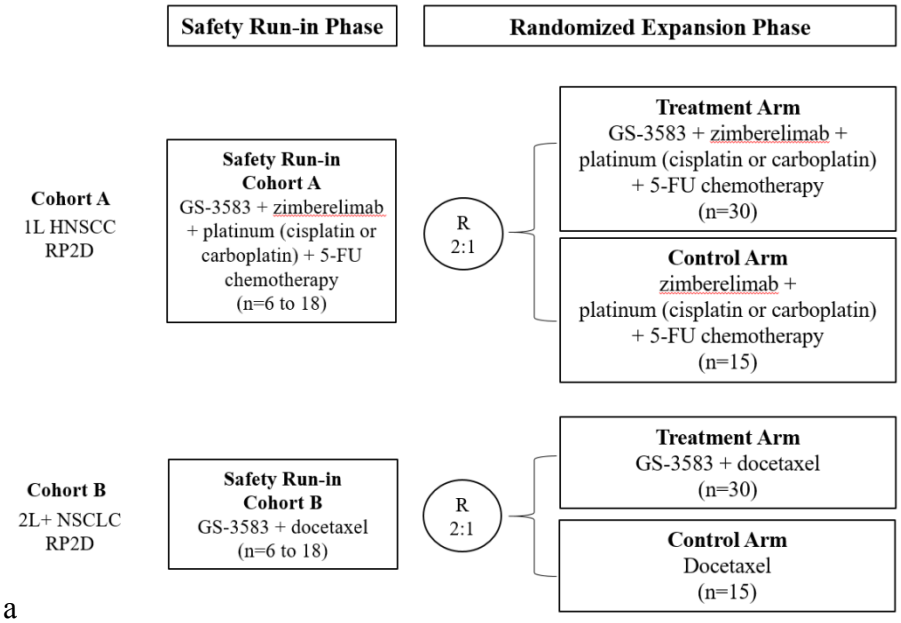


Figure 3-4. Part 2 Safety Run-in and Randomized Expansion Phases



a

5-FU = 5-fluorouracil; HNSCC = head and neck squamous cell carcinoma; NSCLC = non–small-cell lung cancer; RP2D = recommended Phase 2 dose

3.2.3.1. Safety Run-in Cohorts

Initially, 6 subjects will be enrolled into the safety run-in for each cohort at the RP2D as determined in Part 1. A DLT evaluation period of 1 cycle (21 days) will occur.

To date no dose-dependent toxicities have been observed with GS-3583; however, if DLTs occur during the safety run-in, dose de-escalation may take place for GS-3583 using the following rules:

- If no more than 1 of 6 DLT-evaluable subjects experience a DLT in Cycle 1, enrollment into randomized expansion Cohorts A and B may begin at this dose level.
- If 2 subjects experienced DLTs, 3 additional subjects may be enrolled into the cohort at the same dose level. If no additional DLTs occur in these 3 subjects, the dose level may be deemed safe by the SRT. If 1 or more DLTs occur in these 3 subjects, a lower dose cohort will be evaluated using the same 6 + 3 de-escalation algorithm to define the recommended dose for the combination regimens (Table 3-2).
- If 3 or more (> 34%) DLT-evaluable subjects experience a DLT at any time, another 6 subjects may be enrolled at a lower dose (Table 3-2) and will be evaluated in the same manner to define the recommended dose for the combination regimen.

The definitions of hematological and nonhematological toxicities in Section 3.2.2 will be utilized for Part 2.

Table 3-2. Safety Run-in Cohort A: Dose De-escalation

Dose Level	Drug/Dose/Route	Dose Schedule (Day per 21-Day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
Starting dose	GS-3583 RP2D IV (60 min ± 10 min)	Day 1	Day 1	Day 1 (Maximum of 8 cycles[a])
	Zimberelimab 360 mg IV (60 min ± 5 min)	Day 1	Day 1	Day 1 (for up to 105 weeks[b])
	5-FU 1000 mg/m^2 of BSA/day continuous IV over 96 hours[c]	Days 1-4	Days 1-4	Days 1[d]-4 Cycles 3-6 (Maximum of 6 cycles)
	Cisplatin 100 mg/m^2 of BSA[e] IV (1 hour[f]) or Carboplatin AUC of 5 mg/mL/min (1 hour[f])	Day 1	Day 1	Day 1 Cycles 3-6 (Maximum of 6 cycles)
Level minus 1	GS-3583 Dose Level minus 1[g] IV (60 min ± 10 min)	Day 1	Day 1	Day 1 (Maximum of 8 cycles[a])
	Zimberelimab 360 mg IV (60 min ± 5 min)	Day 1	Day 1	Day 1 (for up to 105 weeks[b])
	5-FU 1000 mg/m^2 of BSA/day continuous IV over 96 hours[c]	Days 1-4	Days 1-4	Days 1[d]-4 Cycles 3-6 (Maximum of 6 cycles)
	Cisplatin 100 mg/m^2 of BSA[e] IV (1 hour[f]) or Carboplatin AUC of 5 mg/mL/min (1 hour[f])	Day 1	Day 1	Day 1 Cycles 3-6 (Maximum of 6 cycles)

BSA = body surface area; 5-FU = 5-fluorouracil; IV = intravenous; RP2D = recommended Phase 2 dose

a Subjects will receive GS-3583 for an additional 2 cycles after the completion of chemotherapy. This will amount to a maximum of 8 cycles of GS-3583 since there will be a maximum of 6 cycles of chemotherapy. Should the chemotherapy be terminated prior to the completion for Cycle 6 (due to reasons other than disease progression), GS-3583 will be continued for an additional 2 cycles.

b Zimberelimab treatment will continue for a maximum of 105 weeks, unless 1 or more criteria for discontinuation are met.

c l-leucovorin or d,l-leucovorin may be given prior to infusion according to local practice.

d On Day 1 of each treatment cycle, the 5-FU infusion should be started after completion of all procedures and assessments according to the schedule of assessments (Appendix 4).

e Dosing may be modified based on local/regional label and practice.

f Or infusion duration according to local practice.

g Refer to Table 3-1 for GS-3583 dose levels.

Table 3-3. Safety Run-in Cohort B: Dose De-escalation

Dose Level	Drug/Dose/Route	Dose Schedule (Day per 21-Day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
Starting dose	GS-3583 RP2D IV (60 min ± 10 min)	Day 1	Day 1	Day 1[a] (Maximum of 8 cycles)
	Docetaxel 75 mg/m^2 of BSA IV (60 min ± 10 min)[b,c]	Day 1	Day 1	Day 1
Level minus 1	GS-3583 Dose Level minus 1[d] IV (60 min ± 10 min)	Day 1	Day 1	Day 1[a] (Maximum of 8 cycles)
	Docetaxel 75 mg/m^2 of BSA IV (60 min ± 10 min)[b,c]	Day 1	Day 1	Day 1

BSA = body surface area; IV = intravenous; RP2D = recommended Phase 2 dose
a GS-3583 will be given for a maximum of 8 cycles. Should docetaxel be terminated prior to Cycle 6 (due to reasons other than disease progression), GS-3583 will be continued for an additional 2 cycles.
b Docetaxel treatment is not limited by number of cycles and will continue until 1 or more criteria for discontinuation are met.
c GS-3583 will be administered before the start of the docetaxel infusion.
d Refer to Table 3-1 for GS-3583 dose levels.

DLT Assessment Period: The DLT assessment period for Part 2 will be the first cycle (21 days) and applies to each safety run-in cohort. Subjects will be considered evaluable for assessment of DLTs if either of the following criteria is met during the DLT assessment period:

- The subject experiences a DLT at any time after initiation of the first infusion of GS-3583.
- The subject does not experience a DLT and completes at least 1 infusion of GS-3583 and at least 1 dose of zimberelimab, 1 dose of 5-FU, and 1 dose of cisplatin for safety run-in Cohort A; at least 1 infusion of GS-3583 and 1 dose of docetaxel for safety run-in Cohort B.

If a subject experiences a DLT during the DLT assessment period, the subject will discontinue treatment. Subjects who are not evaluable for DLT assessment in the safety run-in cohorts will be replaced.

3.2.4. Safety Review Team

An SRT will be established to assess safety, review available PK data, make decisions on dose escalation, including the decision to dose escalate and the dose to be evaluated, and define the DLT and MTD, if applicable. The SRT will consist of at least 1 investigator, a representative from Gilead Global Patient Safety (GLPS) and the Gilead medical monitor. Others may be invited to participate as members of the SRT if additional expertise is desired (ie, representatives from Clinical Operations, Biostatistics, Clinical Pharmacology, and Biomarkers Sciences). The medical monitor serves as the chair of the SRT. An SRT charter will be agreed on by all SRT members prior to the first SRT meeting. The data reviewed at the SRT meeting to make dose-escalation decisions will be defined in the SRT charter. The quality control checks performed on the data reviewed and used for making dose-escalation decisions will be described in the SRT charter.

3.3. Study Treatments

Details of on-study treatments administered in this study are described in Section 5. Refer to Section 5.3 for description of study drug formulation and packaging, Section 5.4 for details on planned doses to be administered, timing of doses, and any required pre- or post-medication and prophylaxis, Section 5.5 for instructions with regards to dose modifications and treatment interruptions, and Section 5.6 for information about prior and concomitant medications.

3.4. Duration of Treatment

During Part 1 of the study, GS-3583 will be administered for a maximum of 13 cycles.

During Part 2 of the study, GS-3583 will be administered for a maximum of 8 cycles as follows:

- In Cohort A (HNSCC), subjects will receive GS-3583 for an additional 2 cycles after the completion of chemotherapy. This will amount to a maximum of 8 cycles of GS-3583 since there will be a maximum of 6 cycles of chemotherapy. Should the chemotherapy be terminated prior to Cycle 6 (due to reasons other than disease progression), GS-3583 will be continued for an additional 2 cycles.

- In Cohort B (NSCLC), docetaxel will be given until 1 or more criteria for discontinuation are met; and not limited by number of cycles. For these subjects, GS-3583 will be given for a maximum of 8 cycles. Should docetaxel be terminated prior to Cycle 6 (due to reasons other than disease progression), GS-3583 will be continued for an additional 2 cycles.

In Part 2 Cohort A, zimberelimab may be administered for up to 105 weeks.

Subjects will be treated with study drug until they meet discontinuation of study treatment listed in Section 6.10.1.

In Part 2, subjects who prematurely discontinue GS-3583 may be able to continue other study drugs and remain on the study if they are deemed to continue to derive benefit from those agents. However, such cases must be discussed with and approved by the medical monitor.

3.4.1. Treatment Beyond Initial Progressive Disease

Pseudoprogression has been observed with CPI immunotherapeutic agents such as GS-3583 and zimberelimab which can differ from responses seen with cytotoxic agents and can manifest as a clinical response after an initial transient increase in tumor burden or appearance of new lesions.

Subjects who experience initial radiologic progressive disease and are clinically worsened will discontinue study drug treatment(s) and no further imaging is required.

Subjects who experience initial radiologic progressive disease but improve clinically are considered to have initial response evaluation criteria in solid tumors Version 1.1 (RECIST V1.1)–defined progressive disease and will be permitted, in consultation with the medical monitor, to continue with study drug treatment(s). These subjects will be reevaluated using the

same imaging modality no less than 4 weeks later (after the last imaging with initial RECIST V1.1–defined progressive disease) to assess whether study drug treatment will be continued. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating radiologic progressive disease, treatment may be continued as per treatment calendar. If repeat imaging confirms radiologic progressive disease, subjects will be discontinued from study therapies. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as nontarget lesions.

To continue study drug treatment beyond initial RECIST V1.1–defined progressive disease, subjects must meet all the following criteria:

- There is investigator-assessed clinical benefit from the study drug treatment
- Subject is clinically stable
- Subject is tolerating study drug, and
- There is an agreement with Gilead

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued study drug treatment. The following criteria need to be taken into consideration:

- Absence of clinical symptoms and signs (including worsening of laboratory values) indicating progressive disease,
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status attributed to underlying malignancy, and
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention.

3.4.2. Subsequent Anticancer Therapy

The investigator or qualified designee will review all new anticancer therapy initiated after the last dose of study treatment. If a subject initiates a new anticancer therapy within 60 days after the last dose of study treatment, the 60-day follow-up visit must occur before the first dose of the new anticancer therapy.

3.5. Study Discontinuation Criteria

A subject will be discontinued from the study for any of the following reasons:

- Withdrawal of consent
- Investigator’s discretion

- Death
- Lost to follow-up
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an institutional review board (IRB), or independent ethics committee (IEC)

3.6. End of Study

End of study will be defined as when the last subject reaches the last scheduled follow-up time point (including the 60-day follow-up or survival follow-up, whichever occurs the latest), or is lost to follow-up, withdraws from the study, death, or the time at which Gilead closes the study.

3.7. Poststudy Care

Upon discontinuation from study treatment, subjects will receive the care upon which they and their physician(s) agree. Subjects will be followed for survival and AEs as specified in Section 7.3.2 and 7.3.3.

3.8. Source Data

The source data for this study will be obtained from electronic data capture (EDC), interactive voice/web response system (IXRS), central laboratory, and specialty laboratory (for PK, immunogenicity and/or pharmacodynamic data).

3.9. Biomarker Testing

3.9.1. Biomarker Samples to Address the Study Objectives

The following biological specimens will be collected from all subjects who have provided consent to participate in this study and may be used to evaluate the association of systemic and/or tissue-based biomarkers with study drug response (including efficacy and/or AEs) and dose selection, and to better understand the biological pathways involved in response to GS-3583, to increase knowledge and understanding of the biology of solid tumors and/or to validate a companion diagnostic. Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it may not be possible to specify prospectively all tests that may be done on the specimens provided. The specific analyses will include, but may not be limited to, the biomarkers and assays listed below. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of study to remove tests no longer indicated and/or to add new tests based upon new state of the art knowledge.

Samples will be collected to measure biomarkers that may include but will not be limited to:

- Whole blood samples to prepare peripheral blood mononuclear cells (PBMCs) for analysis of DCs, monocytes, and natural killer (NK) cells by flow cytometry, an analysis of additional immune cells such as T cells and relevant activation markers by cytometry by time-of-flight (CyTOF) and single cell RNA sequencing. Additionally, plasma will be prepared from these samples for analysis of circulating factors such as cytokines.
- Whole blood samples for blood cell count
- Whole blood samples for analysis of mutations associated with clonal hematopoiesis of indeterminate potential (CHIP)
- Whole blood samples for T-cell receptor (TCR) sequencing to analyze immune repertoire changes
- Whole blood samples for analysis of circulating tumor DNA
- Whole blood samples (Paxgene RNA) for blood cell gene expression analysis
- Serum samples for analysis of circulating factors such as cytokines
- Stool samples for microbiome sequencing
- Archival tumor tissue biopsy for analysis of tumor mutations, provided as formalin-fixed paraffin-embedded (FFPE) blocks or 10 to 25 unstained slides. If archival tumor tissue is not available or insufficient, CCI [redacted].
- Fresh baseline and on-treatment biopsies to assess pharmacodynamic changes in the tumor and changes associated with tumor progression by immunohistochemistry (IHC) and gene expression analysis (Part 2). A recent archival tumor tissue biopsy obtained after finishing the last line of therapy and not older than 6 months may be substituted for the fresh baseline biopsy.

In addition to the study-specific informed consent to be signed by each subject participating in the study, a separate, specific consent will be required to document a subject's agreement to provide fresh tumor biopsy samples. CCI [redacted]

CCI [redacted]

The specimens collected will be used to assess expansion of DCs and T cells in the tumor by IHC and gene expression profiling, expression of genes related to immune system activity and tumor biology, and the frequency and identity of tumor mutations.

3.9.2. Biomarker Samples for Optional Future Research

CCI [redacted]

3.9.3. Biomarker Samples for Optional Genomic Research

CCI [redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

This study will enroll approximately 150 subjects with advanced solid tumors as follows:

Part 1: 24 subjects

Part 2 Safety Run-in Cohort A: 6 to 18 subjects

Part 2 Safety Run-in Cohort B: 6 to 18 subjects

Part 2 Randomized Expansion Cohort A: approximately 45 subjects (randomized 2:1)

Part 2 Randomized Expansion Cohort B: approximately 45 subjects (randomized 2:1)

4.1.1. Target Population

Part 1: Adult subjects aged ≥ 18 years with a histologically or cytologically confirmed diagnosis of locally advanced or metastatic malignant solid tumor that is refractory to or intolerant of standard therapy or for which no standard therapy is available.

Part 2:

- Cohort A (HNSCC): Adult subjects aged ≥ 18 years with a histologically or cytologically confirmed diagnosis of metastatic HNSCC who have not previously received systemic therapy for metastatic disease or with recurrent disease who were considered incurable by local therapies.

- Cohort B (NSCLC): Adult subjects aged ≥ 18 years with a histologically or cytologically confirmed locally advanced or metastatic NSCLC with documented progression on at least one anti-PD-1 or anti-PD-L1 mAb and platinum chemotherapy given individually or in combination.

4.1.2. Subject Replacement

During Part 1 and during safety run-in of Part 2, any subject who fails to receive all GS-3583 treatments or fails to complete all safety assessments in the DLT period for reasons other than DLT will be replaced.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in Part 1 or Part 2 of this study:

1) Voluntarily agree to participate by giving a signed written informed consent

2) Age ≥ 18 years

3) Have measurable disease on imaging based on RECIST Version 1.1 (Appendix 7). Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. Historical images within 28 days of the screening visit may be accepted as a screening image if deemed acceptable in the opinion of the investigator.

4) Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 for Part 1 and ECOG of 0-1 for Part 2

5) Diagnosis

   a) **Part 1:** Histologically or cytologically confirmed diagnosis of locally advanced or metastatic malignant solid tumor that is refractory to or intolerant of standard therapy or for which no standard therapy is available

   b) **Part 2 Cohort A (HNSCC):**

      i) Subjects must have histologically or cytologically confirmed recurrent or metastatic HNSCC that is considered incurable by local therapies.

      ii) Subjects should not have had prior systemic therapy administered in the recurrent or metastatic setting. Systemic therapy which was completed more than 6 months prior to signing consent if given as part of multimodal treatment for locally advanced disease is allowed.

      iii) The eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx.

      iv) Subjects with a primary tumor site of nasopharynx (any histology) are not allowed.

      v) Subjects must provide adequate tissue for biomarker analysis at baseline (fine needle aspirate [FNA] is not adequate). Repeat samples may be required if adequate tissue is not provided. This specimen may be the diagnostic sample for subjects with a new diagnosis of metastatic HNSCC. If obtained for a subject with recurrent disease for locally advanced disease, then it must be obtained after completion of the previous initial management with no other treatment from the time of biopsy until the start of study treatment. Subjects must also have a CPS at baseline using a locally available, validated test.

         Note: In Randomized Expansion Cohort A, no more than 10 subjects with CPS < 1 will be enrolled in the Treatment Arm and no more than 5 subjects with CPS < 1 will be enrolled in the Control Arm (Section 3.2.3).

vi) Subjects must have results from local testing of HPV for oropharyngeal cancer defined as p16 IHC testing using a locally available validated test.

Note: Subjects with oral cavity, hypopharynx, or larynx cancer are not required to undergo HPV testing by p16 IHC as by convention they are assumed to be HPV negative.

c) Part 2 Cohort B (NSCLC):

i) Subjects must have histologically or cytologically confirmed locally advanced, unresectable or metastatic NSCLC with documented progression on at least 1 anti-PD-1 or anti-PD-L1 mAb and platinum-based chemotherapy. Anti-PD-1 or anti-PD-L1 mAb and platinum-based chemotherapy may have been given individually or in combination.

ii) Includes subjects who received prior platinum-based chemoradiotherapy (with or without maintenance anti-PD-L1 antibody) for Stage 3 disease. To be considered to have progressed during or after prior treatment with platinum-based chemotherapy, subjects should have either received prior platinum-based chemotherapy in the recurrent or metastatic setting or have experienced disease progression within 6 months of last dose of platinum-based chemotherapy administered as part of concurrent chemoradiation for Stage 3 disease or as neoadjuvant or adjuvant therapy. To be considered to have progressed during or after prior treatment with an anti-PD-1 or anti-PD-L1 antibody, subjects should have either received this therapy in the recurrent or metastatic setting or have experienced disease progression during "maintenance" treatment following concurrent chemoradiation for Stage 3 disease.

These subjects must be tested for epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS1, and PD-L1. Testing for other actionable genomic alterations is recommended and to be performed as per local standard of care.

iii) Subjects with EGFR, ALK, ROS1, or any other known actionable genomic alterations must have also received treatment with at least 1 approved therapy appropriate to the genomic alteration, unless these options are not available to the subjects.

Note: No additional treatments are allowed in the recurrent/metastatic setting for subjects with no actionable genomic alterations.

iv) Documented radiographic disease progression while on or after receiving the most recent treatment regimen for advanced or metastatic NSCLC.

v) Subjects with mixed small-cell lung cancer and NSCLC histology are not eligible.

vi) Subjects must provide adequate tissue for biomarker analysis at baseline (FNA is not adequate). Repeat samples may be required if adequate tissue is not provided. It must be obtained after completion of the previous line of therapy with no other treatment from the time of biopsy until the start of study treatment.

6) Life expectancy of ≥ 3 months, in the opinion of the investigator

7) Adequate organ function as assessed by hematological, renal, and hepatic parameters and no clinically significant coagulopathy as indicated by the following laboratory values (Hematologic laboratory values must be met at screening visit and maintained without transfusional or growth factor support within 2 weeks of study drug initiation):

System	Laboratory Value[a]
Hematological[b]	
Absolute Neutrophil Count (ANC)	≥ 1.5×10^9/L
Platelets[c]	**Part 1 and Part 2 Cohort B (NSCLC):** ≥ 100×10^9/L **Part 2 Cohort A (HNSCC):** ≥ 75×10^9/L
Hemoglobin[c]	**Part 1:** ≥ 8 g/dL (≥ 9.5 g/dL in subjects with cardiac disease) **Part 2:** ≥ 9 g/dL (≥ 9.5 g/dL in subjects with cardiac disease)
Renal	
Creatinine Clearance[c]	**Part 1 and Part 2 Cohort B (NSCLC):** ≥ 50 mL/min by the Cockcroft-Gault method **Part 2 Cohort A (HNSCC):** ≥ 60 mL/min by the Cockcroft-Gault method
Hepatic	
Total Bilirubin	≤ 1.5 × ULN
AST (SGOT) and ALT (SGPT)[c]	**Part 1 and Part 2 Cohort A (HNSCC):** ≤ 3 × ULN (≤ 5 × ULN in subjects with liver metastases) **Part 2 Cohort B (NSCLC):** ≤ 2.5 × ULN (≤ 5 × ULN in subjects with liver metastases)
Serum albumin[c]	**Part 2 Cohort B (NSCLC) only:** > 3 g/dL
Coagulation[d]	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤ 1.5 × ULN unless the subject is receiving anticoagulant therapy
Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 × ULN unless the subject is receiving anticoagulant therapy

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal

a All screening laboratory tests must be reviewed by the investigator and be acceptable prior to enrollment.

b Hematologic laboratory values must be met at screening visit and maintained without transfusional or growth factor support within 2 weeks of study drug initiation.

c Adequate laboratory values differ by study part and/or cohort due to differences in anticancer agents used in Part 2.

d Subjects on full-dose oral anticoagulation, must be on a stable dose (minimum duration 14 days prior to the screening visit). Subjects on low molecular weight heparin will be allowed. In subjects receiving warfarin, the recommended INR is ≤ 3.0 with no active bleeding (ie, no bleeding within 14 days prior to first dose of study drug).

8) A negative serum pregnancy test is required for female subjects (unless permanently sterile or greater than 2 years postmenopausal as described in Appendix 5).

9) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception and refrain from egg or sperm donation as described in Appendix 5.

10) All acute toxic effects of prior antitumor therapy resolved to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Grade ≤ 1 before the first dose of study drug, with the exception of Grade 2 alopecia and peripheral neuropathy.

11) Lactating females must agree to discontinue nursing before the study drug is administered until 12 weeks after the last dose of study drug.

12) Able and willing to comply with the protocol requirements

4.3. Exclusion Criteria

4.3.1. General Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not eligible to be enrolled in Part 1 or Part 2 of this study:

1) Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 3 weeks of the first dose of treatment

2) Has received prior systemic cytotoxic chemotherapy, biological therapy, radiotherapy, or major surgery within 3 weeks of Cycle 1 Day 1; a 1-week washout is permitted for palliative radiation to non–central nervous system (CNS) disease with medical monitor approval

3) Is expected to require any other form of systemic or localized anticancer therapy while on study (including maintenance therapy with another agent, and/or surgical resection); for subjects enrolled in Part 1 of the study, provision of SBRT per local standard of care is acceptable beyond the DLT evaluation period starting at Cycle 2. Hormonal/endocrine therapy for prostate cancer or breast cancer is permitted.

4) Has known severe hypersensitivity reactions (NCI CTCAE Grade ≥ 3) to fully human mAb s or fusion proteins, GS-3583 formulation excipients, or severe reaction to immuno-oncology agents, such as colitis or pneumonitis requiring treatment with corticosteroids, any history of anaphylaxis, or uncontrolled asthma

5) Is receiving systemic corticosteroid therapy 1 week prior to the first dose of study treatment or receiving any other form of systemic immunosuppressive medication

Note: The following corticosteroid uses are permitted: use as premedication for known hypersensitivity reactions (eg, IV contrast, IV drug infusions); intraocular, intranasal, inhaled, and/or topical corticosteroids; and/or prednisone at doses of up to 10 mg per day or equivalent. The use of physiologic doses of corticosteroids may be approved after consultation with the medical monitor.

6) Has concurrent active malignancy other than nonmelanoma skin cancer, carcinoma in situ of the cervix, or superficial bladder cancer who has undergone potentially curative therapy with no evidence of disease. Subjects with other previous malignancies are eligible if disease free for > 2 years.

7) Previous history of hematological malignancy, monoclonal gammopathy of unknown significance (MGUS) or other preleukemic states (Presence of CHIP/age-related clonal hematopoiesis [ARCH] is acceptable.)

8) Has a known CNS metastasis(es), unless metastases are treated and stable and the subject does not require systemic corticosteroids for management of CNS symptoms at least 1 week prior to study treatment. Subjects with history of carcinomatous meningitis are excluded regardless of clinical stability.

9) Has active autoimmune disease that requires systemic treatment (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs)

   Note: Subjects with diabetes type 1, vitiligo, psoriasis, hypothyroid disease, or hyperthyroid disease, not requiring immunosuppressive treatment are eligible.

10) Has had an allogeneic tissue/solid organ transplant

11) Has evidence of active pneumonitis

12) Has a serious systemic fungal, bacterial, viral, or other infection that is not controlled or requires IV antibiotics

13) Previously known or existing FLT3 mutation of any kind

14) Has known active hepatitis B virus (HBV) and/or hepatitis C virus (HCV), and/or HIV

    a) Subjects must be negative for hepatitis B surface antigen and total antibody against hepatitis B core antigen (anti-HBc). For subjects where total anti-HBc is positive, HBV DNA by quantitative polymerase chain reaction will be required.

    b) Subjects must be negative for HCV antibody. For subjects with positive HCV antibody, HCV RNA by quantitative polymerase chain reaction will be required.

    c) Subjects must also be negative for HIV at screening.

15) Subjects with cardiovascular disease/abnormalities will be excluded per the following criteria:

    a) Has clinically significant (ie, active) cardiovascular disease: cerebral vascular accident/stroke or myocardial infarction within 6 months of enrollment, unstable angina, congestive heart failure (New York Heart Association class III or IV), or serious uncontrolled cardiac arrhythmia requiring medication.

    b) Has systolic dysfunction defined as ejection fraction < 45% measured by echocardiogram (ECHO) (or multigated acquisition [MUGA] scan). Results from ECHO or MUGA scan performed up to 30 days prior to enrollment are acceptable.

16) History or evidence of clinically significant disorder, condition, laboratory abnormality, or disease that, in the opinion of the investigator or medical monitor would pose a risk to subject safety or interfere with the study evaluations, procedures, or completion

17) Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study

18) Is legally incapacitated or has limited legal capacity

19) Uncontrolled intercurrent illness or significant illnesses during the screening period

20) Part 2 Cohort A HNSCC

    a) Has disease that is suitable for local therapy administered with curative intent

    b) Has progressive disease (PD) within 6 months of completion of curatively-intended systemic treatment for locoregionally advanced HNSCC

21) Part 2 Cohort B NSCLC

    a) Previously received treatment with docetaxel as monotherapy or in combination with other agents

    b) NSCLC that is eligible for definitive local therapy alone

22) Have received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu and COVID-19 vaccines that do not contain live virus are permitted.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment/Randomization

An IXRS will be employed to manage the conduct of the study. The IXRS will be used to maintain a central log documenting enrollment, to assess current inventories of study drug, to initiate any necessary resupply of study drug, and to document discontinuation of study drug. Subjects who meet eligibility criteria will be enrolled starting on Cycle 1 Day 1 and assigned a subject number by IXRS.

For Part 1, no randomization procedures will be applied to treatment assignment.

For Part 2, subjects enrolled in Safety Run-In Cohort A and Safety Run-In Cohort B will not be randomized. After the safety run-in, central randomization will be implemented to minimize bias in the assignment of subjects to treatment groups for expansion Cohort A and Cohort B, respectively. Subjects who meet randomization eligibility criteria will be randomized in a 2:1 ratio to receive GS-3583 in combination with zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy or zimberelimab and platinum (cisplatin or carboplatin) + 5-FU chemotherapy in randomized expansion Cohort A, or to receive GS-3583 in combination with docetaxel or docetaxel alone in randomized expansion Cohort B. The IXRS will implement a randomization scheme and assign a unique subject number.

5.2. Blinding

Not applicable.

5.3. Description and Handling

5.3.1. GS-3583

5.3.1.1. Formulation

GS-3583 is supplied in 2 presentations as a liquid or a lyophilized drug product and intended for IV administration. For Part 1, GS-3583 is supplied either as a liquid or as a lyophilized drug product; for Part 2, GS-3583 is supplied as a liquid drug product. The two formulations are detailed below:

1) GS-3583 Injection is formulated as a sterile, clear, preservative-free liquid composed of 20 mM histidine/histidine-HCl, 263 mM sucrose, and 0.02% (weight-to-volume ratio [w/v]) polysorbate 80 at pH 5.9. It is supplied in a 6 mL vial with a deliverable volume of 5 mL containing 10 mg of GS-3583 at a concentration of 2 mg/mL.

2) GS-3583 lyophilized powder for reconstitution is composed of 20 mM histidine/histidine-HCl, 263 mM sucrose, and 0.02% w/v polysorbate 80 at pH 5.9. It is supplied in a 20 mL vial with a deliverable volume after reconstitution with sterile water for injection of 5 mL containing 10 mg of GS-3583 at a concentration of 2 mg/mL.

5.3.1.2. Packaging and Labeling

GS-3583 will be provided in single-use clear glass vials, closed with coated elastomeric stoppers, and sealed with aluminum overseals and polypropylene flip-off caps.

All labels for GS-3583 drug products to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, European Union (EU) Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.3.1.3. Storage and Handling

GS-3583 must be stored at 2 °C to 8 °C and protected from light. Storage conditions are specified on the study drug label. Until dispensed to the subject, all study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure stability and proper identification, the study drug should be stored in the containers in which they were supplied until dosing the subject.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3.2. Zimberelimab

5.3.2.1. Formulation

Zimberelimab is formulated as a sterile, clear, preservative-free liquid intended for IV administration containing 20 mM histidine/histidine-HCl buffer solution (pH 5.5), 150 mM sucrose, 45 mM sodium chloride, and 0.02% (w/v) polysorbate 80. Each vial is manufactured to ensure a deliverable volume of 4 mL containing 120 mg of zimberelimab at a concentration of 30 mg/mL.

5.3.2.2. Packaging and Labeling

Zimberelimab is supplied in single-use, 8-mL glass vials with rubber stoppers and aluminum crimp overseals with a flip-off cap.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.3.2.3. Storage and Handling

Zimberelimab must be stored at 2 °C to 8 °C (36 °F to 46 °F). Zimberelimab should not be frozen. Protect from light during storage. Do not shake. Storage conditions are specified on the label. Until dispensed to the subject, study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3.3. Cisplatin

5.3.3.1. Formulation

Cisplatin is commercially sourced. Information regarding the formulation can be found in the current prescribing information or summary of product characteristics for each country where the study will be conducted.

5.3.3.2. Packaging and Labeling

Commercial product of cisplatin will be used for this study. Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.3.3.3. Storage and Handling

Information regarding the storage and handling of cisplatin can be found in the current prescribing information.

5.3.4. Carboplatin

5.3.4.1. Formulation

Carboplatin is commercially sourced. Information regarding the formulation can be found in the current prescribing information or summary of product characteristics for each country where the study will be conducted.

5.3.4.2. Packaging and Labeling

Commercial product of carboplatin will be used for this study. Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.3.4.3. Storage and Handling

Carboplatin is commercially sourced. Further information regarding storage and handling can be found in the current country-specific prescribing information.

5.3.5. 5-Fluorouracil

5.3.5.1. Formulation

5-FU is commercially sourced. Information regarding the formulation can be found in the current prescribing information or summary of product characteristics for each country where the study will be conducted.

5.3.5.2. Packaging and Labeling

Commercial product of 5-FU will be used for this study. Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.3.5.3. Storage and Handling

5-FU is commercially sourced. Information regarding the storage and handling can be found in the current prescribing information.

5.3.6. Docetaxel

5.3.6.1. Formulation

Docetaxel is commercially sourced. Information regarding the formulation can be found in the current full prescribing information or summary of product characteristics for each country where the study will be conducted.

5.3.6.2. Packaging and Labeling

Commercial product of docetaxel will be used for this study where docetaxel is approved for the treatment of locally advanced or metastatic NSCLC after platinum therapy failure. Study drug to be distributed to centers in other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.3.6.3. Storage and Handling

Docetaxel is commercially sourced. Information regarding the storage and handling can be found in the current prescribing information.

5.4. Dosage and Administration

5.4.1. GS-3583

GS-3583 will be administered as an IV infusion over 60 (± 10) minutes. The proposed doses of GS-3583 for Part 1 of the study are 675 µg, 2000 µg, 6000 µg, 12,000 µg, and 20,000 µg; intermediate doses within this range may also be evaluated. The recommended dose for Part 2 will be determined based on the safety, PK, pharmacodynamics, and all other relevant data from Part 1 and will not exceed the MTD in Part 1.

In Part 1, the proposed dosing frequency is GS-3583 administered on Days 1 and 15 of Cycle 1 and on Day 1 of each subsequent 4-week/28-day cycle; up to a maximum of 13 cycles.

In Part 2 Safety Run-in Cohorts and Treatment Arms of the Randomized Expansion Cohorts, the proposed dosing frequency is GS-3583 administered on Day 1 of each 3-week/21-day cycle up to a maximum of 8 cycles (Table 5-1).

Table 5-1. Proposed Schedule for GS-3583 in Part 1 and Part 2 of the Study

	Cycle 1[a]	Subsequent Cycles[a]
Part 1	Days 1 and 15	Day 1 (up to 13 cycles)
Part 2 Cohorts A[b] and B[c]	Day 1	Day 1 (up to 8 cycles)

a In Part 1, each cycle is 28 days; in Part 2, each cycle is 21 days.
b In Part 2 Cohort A (Safety Run-in Cohort and Randomized Expansion Cohort Treatment Arm), subjects will receive GS-3583 for an additional 2 cycles after the completion of chemotherapy. This will amount to a maximum of 8 cycles of GS-3583 since there will be a maximum of 6 cycles of chemotherapy. Should the chemotherapy be terminated prior to Cycle 6 (due to reasons other than disease progression), GS-3583 will be continued for an additional 2 cycles.
c In Part 2 Cohort B (Safety Run-in Cohort and Randomized Expansion Cohort Treatment Arm), GS-3583 will be given for a maximum of 8 cycles. Should docetaxel be terminated prior to Cycle 6 (due to reasons other than disease progression), GS-3583 will be continued for an additional 2 cycles.

Premedications should not be administered routinely prior to dosing of GS-3583 unless a previous infusion reaction occurred. Refer to Section 5.5.1.3 for subsequent premedication recommendations following GS-3583–related infusion reactions.

GS-3583 should be administered IV over approximately 60 minutes (± 10 minutes) at the research clinic by a qualified staff member. Infusions will be followed immediately with a saline flush of the IV line, per institutional guidelines. Modifications of the infusion rate due to infusion-related reactions are described in Section 5.5.1.3 and Table 5-4. The study drug will be administered without regard to food.

Subjects receiving GS-3583 should be monitored for infusion-related reactions. This includes the measurement of vital signs prior to each infusion commencing and at the end of each infusion (Table 5-2). In Part 1, vital signs will also be measured 1 hour (± 15 minutes) after the end of the GS-3583 infusion for the first 2 doses during Cycle 1. Thereafter in subsequent cycles, the posttreatment vital signs can be taken 30 minutes (−10/+20 minutes) after the end of the GS-3583 infusion. In Part 2 Cohorts A and B, vital signs will also be measured 1 hour (± 15 minutes) after the end of the GS-3583 infusion for the first dose during Cycle 1. Thereafter in subsequent cycles, the posttreatment vital signs can be taken 30 minutes (−10/+20 minutes) after the end of the GS-3583 infusion. Subjects will remain in the clinic under close supervision for the duration of this monitoring period.

Table 5-2. Schedule for Measurement of Vital Signs in Part 1 and Part 2 of the Study

	Cycle 1[a], Day 1	Cycle 1[a], Day 15	Subsequent Cycles[a], Day 1
Part 1	preinfusion, end of infusion; 1 hour (± 15 minutes) postinfusion	preinfusion, end of infusion; 1 hour (± 15 minutes) postinfusion	preinfusion, end of infusion; 30 minutes (−10/+20 minutes) postinfusion
Part 2 Cohorts A and B	preinfusion, end of infusion; 1 hour (± 15 minutes) postinfusion	—	preinfusion, end of infusion; 30 minutes (−10/+20 minutes) postinfusion

a In Part 1, each cycle is 28 days; in Part 2, each cycle is 21 days

5.4.2. Combination Therapies

Planned dosage and administration of combination therapies is shown in Table 5-3. GS-3583 will be administered as described in Section 5.4.1. Further details on dosing, including recommended premedications is provided in Sections 5.4.2.1 (zimberelimab), 5.4.2.2 (cisplatin or carboplatin), 5.4.2.3 (5-FU), and 5.4.2.4 (docetaxel).

On days when GS-3583 is coadministered with other therapies, GS-3583 will be administered first. There will be a minimum of 1-hour observation period between the completion of GS-3583 infusion and the start of the next agent/therapy or their corresponding premedication.

Table 5-3. Proposed Dose Levels and Schedules of Combination Therapies for Randomized Disease-Specific Expansion Cohorts

Cohort Number	Disease-specific Cohort	Drug/Dose/Route	Dose Schedule (Each Cycle is 21 Days)
Cohort A	Metastatic or unresectable, recurrent HNSCC	Zimberelimab 360 mg IV infusion over 60 min ± 5 min	Day 1 of each cycle (up to 105 weeks)[a]
		Cisplatin 100 mg/m² of BSA IV infusion over 1 hour[b]	Day 1 of each cycle (up to 6 cycles)
		Carboplatin AUC 5 mg/mL/min IV given over 1 hour[b]	Day 1 of each cycle (up to 6 cycles)
		5-FU 1000 mg/m² of BSA/day continuous IV infusion over 96 hours	Day 1[c] to Day 4 of each cycle (up to 6 cycles)
Cohort B	Locally advanced, unresectable or metastatic NSCLC[d]	Docetaxel 75 mg/m² of BSA IV infusion over 60 min ± 10 min	Day 1 of each cycle[e]

BSA = body surface area; 5-FU = 5-fluorouracil; HNSCC = head and neck squamous cell carcinoma; IV = intravenous; mAb = monoclonal antibody; NSCLC = non–small-cell lung cancer; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death protein 1

a Zimberelimab treatment will continue for a maximum of 105 weeks, unless 1 or more criteria for discontinuation are met.
b Or infusion duration according to local practice.
c On Day 1 of each treatment cycle, the 5-FU infusion should be started after completion of all procedures and assessments according to the Study Procedures Tables (Appendix 4).
d With documented progression on at least one anti-PD-1 or anti-PD-L1 mAb and cisplatin-based chemotherapy given individually or in combination.
e Docetaxel treatment will continue until 1 or more criteria for discontinuation are met, and not limited by number of cycles.

5.4.2.1. Zimberelimab

Premedications are recommended for subjects who had infusion-related reactions to a prior zimberelimab infusion (Table 5-5). Subjects may be premedicated 1.5 hours (± 30 minutes) prior to infusion of zimberelimab with 50 mg diphenhydramine orally (or equivalent dose of antihistamine) and/or 500-1000 mg acetaminophen orally (or equivalent dose of antipyretic).

Zimberelimab doses are administered by IV infusion over 60 minutes (± 15 minutes), followed by a 30- to 60-minute observation period, on Day 1 of each 21-day cycle for a maximum of 35 doses. Further guidance and information for the management of zimberelimab is provided in the Pharmacy Manual.

5.4.2.2. Platinum (Cisplatin or Carboplatin)

Subjects may receive adequate pretreatment hydration per institutional guidelines. Premedication for prevention of chemotherapy-induced nausea and vomiting is recommended.

Cisplatin or carboplatin can be administered in Cohort A (Safety Run-in and Randomized Expansion) per investigator choice. The platinum dosing regimen for Cohort A (Safety Run-in and Randomized Expansion) is presented in Table 5-3.

Cisplatin will be administered on Day 1 of each treatment cycle after completion of all procedures and assessments according to the schedule of assessments (Appendix Table 5). Cisplatin is given using an infusion duration of 60 minutes (or infusion duration according to local practice). Cisplatin can be administered for a maximum of 6 cycles. Subjects receiving cisplatin may switch to carboplatin if toxicities occur based on investigator judgment with medical monitor approval.

Carboplatin will be administered on Day 1 of each treatment cycle after completion of procedures and assessments according to the schedule of assessments (Appendix Table 5). Carboplatin is given using an infusion duration of 60 minutes (or infusion duration according to local practice). Carboplatin can be administered for a maximum of 6 cycles. Subjects receiving carboplatin may switch to cisplatin if toxicities occur based on investigator judgment with medical monitor approval.

5.4.2.3. 5-Fluorouracil

Subjects may receive any premedication as indicated per institutional guidelines.

5.4.2.4. Docetaxel

If necessary, subjects may be premedicated with oral corticosteroids per institutional guidelines to reduce the incidence and severity of fluid retention as well as severity of hypersensitivity reactions.

5.5. Dose Modifications and Treatment Delay

If an AE or a laboratory abnormality is attributed to only one study drug, it is at the investigator's discretion to determine if the study drug(s) not attributed to the AE will be withheld based on the investigator's assessment of risk-benefit of withholding one or more study drugs. Subjects who have drug-related toxicities that meet the criteria for dose delay should have study drug treatment delayed until criteria to resume treatment are met. It is recommended to restart study drug treatment at the next scheduled administration.

Part 2 Cohort A:

For cisplatin, carboplatin, and 5-FU, subjects can have up to 2 dose modifications per agent, for toxicities as described in Table 5-9, Table 5-10, Table 5-12, and Table 5-13. If further toxicity occurs or the criteria for resuming treatment are not met, the subject may be discontinued from that drug, but may continue to participate in the study.

If a subject experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity).

If, in the opinion of the investigator, the toxicity is related to the combination of 2 agents, or if the causality is unclear, 1 or both drugs may be reduced or held according to recommended dose modifications. Likewise, if, in the opinion of the investigator, the toxicity is related to the combination of 3 agents, or the causality is unclear, any 1 or more of the 3 agents may be reduced or held according to the recommended dose modifications. If 1 or more study agent(s) are held for toxicity, the schedule for restarting the agent(s) should correspond with the next treatment cycle once the toxicity has resolved according to the recommended guidelines. Subjects who require more than 2 dose modifications as outlined in the corresponding tables below to any particular component of the regimen for toxicities may have that agent discontinued. Any exception to the above recommendations may only be made with the approval of the medical monitor.

Investigators may follow the local label for dose modifications. If a toxicity is not otherwise specified, investigators should refer to the label or local standard of care for dose adjustments. These dose modification decisions must be documented in the subject's study records and in the case report form.

5.5.1. GS-3583

5.5.1.1. Dose Modifications

Intrasubject dose reduction of GS-3583 is not permitted during Part 1 of the study; the need for a dose reduction is considered a DLT, and the subject may be discontinued from treatment. Intrasubject dose modifications of GS-3583 may be permitted once the MTD has been determined and during Part 1 of the study and written approval from the medical monitor should be obtained prior to dose modification/reduction.

For subjects enrolled in Part 2 of the study, dose reductions may be permitted for the treatment of AEs. Approval from the medical monitor should be obtained prior to dose modification/reduction.

5.5.1.2. Treatment Delay

Study treatment may be delayed due to any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants a delay.

Subjects who have drug-related toxicities that meet the criteria for dose delay should have study drug treatment delayed until criteria to resume treatment are met. Subjects who fail to receive 3 or more consecutive doses of GS-3583 due to treatment delay may be discontinued from the study unless agreed otherwise with the Gilead medical monitor.

5.5.1.3. Treatment of Infusion-Related Reactions

Subjects receiving GS-3583 should be monitored for infusion-related reactions. This includes the measurement of vital signs (refer to Section 5.4.1 and Table 5-2 for schedule of vital signs measurements). Subjects will remain in the clinic under close supervision for the duration of this monitoring period. Subjects with mild or moderate infusion-related reactions may receive GS-3583 with close monitoring. Premedication with an antipyretic or antihistamine for subsequent treatment administration may be considered.

Subjects who do not experience any infusion-related reactions of Grade 1 or higher during or after the infusion may be released from monitoring after 1 hour if they are otherwise stable. Subjects with any infusion-related reactions must be managed as per the guidelines in Table 5-4, and monitoring will continue until any infusion-related reactions have abated to less than Grade 1 and at least 1 hour has passed from the completion of the entire infusion and flushing the line.

Should infusion-related reactions be considered a significant safety issue by the SRT, the SRT may decide to recommend premedication with an antihistamine and acetaminophen approximately 30 to 60 minutes before each dose of GS-3583 (eg, 25-50 mg diphenhydramine, 500-1000 mg acetaminophen or equivalent dose of antipyretic). This regimen may be modified based on local treatment standards and guidelines, as appropriate.

All subjects will be given information on and instructions regarding both infusion-related reactions (which are expected to be most likely in the hour after completion of the infusion) and irAEs before leaving the study site.

Table 5-4. GS-3583 Infusion-Related Reactions Management Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dose Administration
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDs], narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to the following: - IV fluids - Antihistamines - NSAIDs - Acetaminophen - Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise, dose administration will be held until symptoms resolve, and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug administration.	Subject may be premedicated prior to infusion with the following: - Diphenhydramine 25-50 mg PO (or equivalent dose of antihistamine) - Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic)
Grade 3 or 4 Grade 3 Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization 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 - Pressor - Corticosteroids - Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further study drug administration.	No subsequent dosing

IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID = nonsteroidal anti-inflammatory drug; PO = orally

5.5.1.4. Management of Potential Immune-Related Adverse Events

Adverse events (both nonserious and serious) associated with drug exposure and consistent with an immune phenomenon may represent an immunologic etiology. Particular attention should be paid to AEs that may be suggestive of potential irAEs. These irAEs may be predicted based on the nature of the study drug, mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Immune-related AEs may be associated with immuno-oncology agents such as GS-3583. An irAE is defined as an AE of unknown etiology, that is potentially associated with study drug exposure and is consistent with an immune-mediated phenomenon. Early recognition and management of irAEs may mitigate severe toxicity. An irAE can occur any time from shortly after the first dose to several months after the last dose of treatment. Such events may consist of persistent rash, diarrhea, colitis, autoimmune hepatitis, pneumonitis, encephalitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions.

The investigator should refer to the ASCO Toxicity Management Guidelines (Appendix 3) and withhold or discontinue GS-3583 accordingly.

5.5.1.5. Criteria to Resume Treatment

Subjects may resume treatment with GS-3583 when drug-related AE(s) resolve(s) to Grade 1 or baseline value, with the following clarifications and certain exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Drug-related Grade 2 pulmonary toxicity or colitis must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment. (Exception: Study treatment does not need to be delayed/interrupted for subjects who experience immune-related hypothyroidism [Grades 1-2].)
- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.

5.5.2. Zimberelimab

5.5.2.1. Dose Modifications

Dose reductions are not permitted. Zimberelimab treatment may be temporarily suspended in subjects experiencing toxicity considered to be related to study treatment.

5.5.2.2. Treatment Delay

Zimberelimab treatment may be temporarily suspended in subjects experiencing toxicity considered to be related to study treatment. If zimberelimab has been withheld for more than 42 days because of toxicity, the subject should be discontinued from zimberelimab. However, zimberelimab can be resumed after being withheld for more than 42 days if the medical monitor agrees that the subject is likely to derive clinical benefit.

5.5.2.3. Treatment of Infusion-related Reactions

Infusion-related reactions may occur during or after administration of zimberelimab. Dose reductions, other than a decrease in the infusion rate, are not allowed. Management guidelines for infusion reactions are displayed in Table 5-5.

Table 5-5. Management of Infusion-related Reactions

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1: Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2: Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	**Stop infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids, antihistamines, NSAIDs, acetaminophen, and narcotics. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping IP infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 to 50 mL/hour). Otherwise, dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further IP administration.**	Subject may be premedicated 1.5 hours (± 30 minutes) prior to infusion of zimberelimab with: • Diphenhydramine 50 mg orally (or equivalent dose of antihistamine) • Acetaminophen 500-1000 mg orally (or equivalent dose of antipyretic)
Grade 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization 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, and epinephrine. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further IP administration.**	No subsequent dosing

IP = investigational product; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID = nonsteroidal anti-inflammatory drug.

5.5.2.4. Management of Potential Immune-related Adverse Events

Treatment modifications of zimberelimab, including dose delays, may be required in the event of treatment-related toxicity. Dose reductions are not permitted. Zimberelimab treatment may be temporarily suspended in subjects experiencing toxicity considered to be related to study treatment. If zimberelimab has been withheld for more than 42 days because of toxicity, the subject should be discontinued from zimberelimab. However, zimberelimab can be resumed after being withheld for more than 42 days if the medical monitor agrees that the subject is likely to derive clinical benefit. Further details on the assessment, evaluation and treatment of toxicities associated with anticancer immunotherapy can be found in the National Comprehensive Cancer Network (NCCN) Guideline on the Management of Immunotherapy-Related Toxicities. Treatment modifications and toxicity management guidelines for zimberelimab are displayed in Table 5-6. All toxicities will be graded according to NCI CTCAE v5.0. In case of doubt, the investigator should consult with the medical monitor.

Table 5-6. Toxicity Management Guidelines for Zimberelimab

Adverse Event	NCI CTCAE Grade	Action	AE Management	Resumption
Pneumonitis	Grade 2	Withhold	• Evaluate subjects with suspected pneumonitis with radiographic imaging • Administer corticosteroids (initial dose: 1-2 mg/kg/day prednisone or equivalent followed by a taper) • Consider augmentation of therapy per NCCN guidelines (eg, infliximab, mycophenolate) if no improvement in 48 hours	• Resume zimberelimab when pneumonitis resolves to Grade ≤ 1 and steroid dose is stable/decreasing at ≤ 10 mg/day (prednisone or equivalent dose)
	Grade 3 or 4 pneumonitis or recurrent Grade 2 pneumonitis	Permanently discontinue		NA
Colitis or Diarrhea	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose: 1-2 mg/kg/day prednisone or equivalent followed by a taper) • Loperamide for 2-3 days • Consider augmentation of therapy per NCCN guidelines (eg, infliximab) if no resolution in 7 days	• Resume zimberelimab when colitis/diarrhea resolves to Grade ≤ 1 and steroid dose is stable/decreasing at ≤ 10 mg/day (prednisone or equivalent dose)
	Grade 4	Permanently discontinue		NA

Adverse Event	NCI CTCAE Grade	Action	AE Management	Resumption
Transaminitis without elevated bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose: 0.5-1 mg/kg/day prednisone or equivalent followed by a taper)	• Resume zimberelimab when transaminases return to baseline and steroid use is stable/decreasing at ≤ 10 mg/day (prednisone or equivalent)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose: 1-2 mg/kg/day prednisone or equivalent followed by a taper)	NA
Transaminitis with elevated bilirubin (except in Gilbert's syndrome)	Grade 1 or 2 blood bilirubin increased	Withhold. Discontinue any potentially hepatotoxic medications. If no resolution, then permanently discontinue	• Evaluate for alternative etiology (viral, drug-induced) • Administer corticosteroids (initial dose: 2 mg/kg/day prednisone or equivalent followed by a taper)	• Resume zimberelimab if, after discontinuation of any potentially hepatotoxic medication, transaminases return to baseline and steroid use is stable/decreasing at ≤ 10 mg/day (prednisone or equivalent)
	Grade 3 or 4 blood bilirubin increased	Permanently discontinue	• Evaluate for alternative etiology (viral, drug-induced) • Administer corticosteroids (initial dose: 1-2 mg/kg/day prednisone or equivalent followed by a taper) • Hepatology consultation if appropriate	NA

Adverse Event	NCI CTCAE Grade	Action	AE Management	Resumption
Pancreatitis	Grade 1	Continue	• IV hydration • Investigate other possible etiologies of elevated amylase/lipase	NA
	Grade 2	Withhold	• IV hydration • Administer corticosteroids (initial dose: 0.5-1 mg/kg/day prednisone or equivalent followed by a taper)	Resume zimberelimab when: • Symptoms no longer present • No radiographic evidence of pancreatic inflammation • Amylase and lipase
	Grade 3 or 4	Permanently discontinue	• IV hydration • Administer corticosteroids (initial dose: 0.5-1 mg/kg/day prednisone or equivalent followed by a taper)	NA
Thyroid disorders	Hypothyroidism (Grades 1 or 2)	Continue	• Consultation with endocrinologist • Levothyroxine therapy: (1.6 mcg/kg or 75 to 100 mcg starting dose, titrated to TSH level within normal limits for age)	NA
	Hypothyroidism (Grades 3 or 4)	Withhold	• Withhold until clinically stable • Permanently discontinue if clinically indicated	• If not permanently discontinue, resume treatment when symptoms no longer present
Thyroid disorders	Hyperthyroidism (Grades 1 or 2)	Withhold if symptomatic (consider continuing if asymptomatic)	• Consultation with endocrinologist	• Resume when symptoms no longer present
	Hyperthyroidism (Grades 3 or 4)	Withhold	• Withhold until clinically stable • Permanently discontinue if clinically indicated	• If not permanently discontinue, resume treatment when symptoms no longer present

Adverse Event	NCI CTCAE Grade	Action	AE Management	Resumption
Hyperglycemia	Fasting glucose ≤ 200 mg/dL	Continue	• Consider consultation with an endocrinologist	NA
	Fasting glucose > 200 mg/dL OR random glucose > 250 mg/dL	Withhold if DKA is present, otherwise continue	• If DKA, withhold immunotherapy and implement anti-DKA measures	• Resume zimberelimab when DKA is resolved (nonketotic) and in consultation with an endocrinologist to monitor for diabetes and related complications
Renal dysfunction (elevated creatinine)	Grade 1	Consider withholding	• Follow serum creatinine	NA
	Grade 2	Withhold	• Administer corticosteroids (initial dose: 0.5-1 mg/kg/day prednisone or equivalent followed by a taper, if other causes of acute renal failure (dehydration, etc) are ruled out	Resume zimberelimab when: • Renal insufficiency resolves to Grade ≤ 1 • Creatinine is stable • Steroid dose is stable/decreasing at ≤ 10 mg/day (prednisone or equivalent dose)
Renal dysfunction (elevated creatinine)	Grade 3 or 4	Permanently discontinue	• Nephrology consultation • Administer corticosteroids (initial dose: 1-2 mg/kg/day prednisone or equivalent followed by a taper) • Consider augmentation of therapy per NCCN guidelines (eg, azathioprine, cyclosporine) is > Grade 2 for > 7 days	NA
Skin adverse reactions	Refer to Table 5-7 for treatment and management of dermatologic toxicity related to zimberelimab.			
Other (may involve any organ system)	Grade 1	Continue	• Institute supportive measures	NA
	Grade 2	Consider withholding if interfering with ADLs	• Administer corticosteroids based on severity of the adverse reaction	• Resume zimberelimab when AE is ≤ Grade 1
	Grade 3 recurrence or Grade 4	Permanently discontinue	• Administer corticosteroids based on severity of the adverse reaction	NA

Adverse Event	NCI CTCAE Grade	Action	AE Management	Resumption
			• Upon improvement to Grade ≤ 1, initiate corticosteroid taper and continue to taper over ≥ 1 month • Systemic immunosuppressants may be considered for subjects whose immune-related adverse reaction could not be controlled with corticosteroids	

ADL = activity of daily life; AE = adverse event; DKA = diabetic ketoacidosis; IV = intravenous; IVIG = intravenous immunoglobulin; NA = not applicable; NCCN = National Comprehensive Cancer Network; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

Table 5-7. Treatment Management Guidelines for Dermatologic Toxicity Associated With Zimberelimab

Adverse Event	Severity	Assessment	Action Taken	AE Management	Resumption
Dermatologic Toxicity (including but not limited to rash, maculo-papular rash, and pruritus)	Grade 1[a]	• Total body skin exam, including mucosa • Assess for history of prior inflammatory dermatologic diseases • Consider biopsy if unusual features	Continue	• Topical emollient • Oral antihistamine for pruritus • Treatment with moderate potency topical steroids to affected areas	NA
	Grade 2[b]	• Total body skin exam, including mucosa • Assess for history of prior inflammatory dermatologic diseases • Consider biopsy if unusual features	• Continue study dose with intensified antipruritic therapy • Consider holding in select cases	• Topical emollient • Oral antihistamine for pruritus • Treatment with moderate to high potency topical steroids to affected areas • If unresponsive to topical, consider prednisone 0.5 mg/kg/day	For the select cases where treatment is held, consider resuming after symptoms have resolved to ≤ Grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 3[c]	• Total body skin exam, including mucosa • Assess for history of prior inflammatory dermatologic diseases • Consider biopsy if unusual features	Withhold	• Treatment with high potency topical steroids to affected areas • Prednisone 0 5 to 1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) • Urgent dermatology consultation, consider biopsy • Consider in-patient care.	Consider resuming after symptoms have resolved to ≤ Grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 4[c]	• Total body skin exam, including mucosa • Assess for history of prior inflammatory dermatologic diseases • Consider biopsy if unusual features	Permanently discontinue	• Treatment with high potency topical steroids to affected areas • Prednisone 0 5 to 1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) • Urgent dermatology consultation, consider biopsy • Consider in-patient care.	Do not resume

Adverse Event	Severity	Assessment	Action Taken	AE Management	Resumption
Dermatologic Toxicity: Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN)[d]	Grade 3	• Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue	• Prednisone or methylprednisolone 1 to 2 mg/kg/day (treat until symptoms improve to ≤ Grade 1 then taper over 4 to 6 weeks). • Consider IVIG (1g/kg/day in divided doses per package insert for 3 to 4 days) • In-patient care required • Urgent dermatology, ophthalmology, and urology consultation	Do not resume
	Grade 4	• Urgent dermatology consultation: if unavailable, consider	Permanently discontinue	• Prednisone or methylprednisolone 1 to 2 mg/kg/day (treat until symptoms improve to ≤ Grade 1 then taper over 4 to 6 weeks). • Consider IVIG (1 g/kg/day in divided doses per package insert for 3 to 4 days) • In-patient care required • Urgent dermatology, ophthalmology, and urology consultation	Do not resume

ADL = activity of daily life; AE = adverse event; BSA = body surface area; DKA = diabetic ketoacidosis; IV = intravenous; IVIG = intravenous immune globulin; NA = not applicable; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

a. Macules/papules covering less than 10% BSA with or without symptoms (eg, pruritis, burning, tightness)
b. Macules/papules covering 10 to 30% BSA with or without symptoms (eg, pruritis, burning, tightness); limiting instrumental ADLs.
c. Macules/papules covering more than 30% BSA with or without symptoms (eg, pruritis, burning, tightness) limiting ADLs.
d. SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving less than 10%, 10 to 30%, and more than 30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and mucous membranes.

Guidelines are referenced from the National Comprehensive Cancer Network (NCCN) Management of Immunotherapy-Related Toxicities Version 4.2021 – September 27, 2021

5.5.2.5. Criteria to Resume Treatment

In the event that zimberelimab is held due to toxicities, criteria for resumption of dosing are outlined in Table 5-6.

5.5.2.6. Permanent Treatment Discontinuation

Criteria for permanent discontinuation of zimberelimab for toxicities are defined in Table 5-6.

5.5.3. Dose Modifications for Platinum (Cisplatin or Carboplatin)

Cisplatin is known to cause nephrotoxicity, peripheral neuropathy, nausea and vomiting, myelosuppression, ototoxicity, and hypersensitivity reactions.

Cisplatin or carboplatin dose delays and resumption of treatment as well as dose reductions and treatment discontinuation decisions should be conducted in accordance with the current local label and treatment guidelines. The cisplatin dose must not be re-escalated following a dose reduction. General platinum dose modification guidelines for febrile neutropenia or documented infection and drug-related AEs are described in Table 5-8, Table 5-9, and Table 5-10; these general guidelines may be overridden by local label and/or treatment guidelines with the approval of the medical monitor. If cisplatin or carboplatin is discontinued for reasons other than disease progression, the remaining drug(s) in the combination regimen may be continued.

If toxicities occur, investigators may switch subjects from cisplatin to carboplatin and vice versa during the course of the study. If the cisplatin dose was modified prior to switching, the subject may start at a carboplatin dose of AUC 5 and will be eligible to receive an additional 2 dose modifications of carboplatin.

Recommended initial dose and dose reductions for cisplatin and carboplatin are detailed in Table 5-8.

Table 5-8. Platinum Dose Modification Levels

	Dose level 0	Dose level −1	Dose level −2	Dose level −3
Cisplatin	100 mg/m^2	80 mg/m^2 (20% decrease)	64 mg/m^2 (20% decrease)	Discontinue
Carboplatin	AUC 5 mg/mL/min	AUC 4 mg/mL/min (20% decrease)	AUC 3 mg/mL/min (20% decrease)	Discontinue

Table 5-9. Platinum Dose Modification Guidelines for Febrile Neutropenia or Documented Infection

Adverse Event	Number of Occurrences	Treatment Modification
Febrile neutropenia[a] Documented infection	1	Reduce by 1 dose level The use of growth factors and antibiotics should be considered per local standards
	2	Reduce by 1 dose level Consider prophylactic antibiotics for subsequent cycles The use of growth factors should be strongly considered per local standards
	3	Discontinue platinum

a Absolute neutrophil count < 1000/mm^3 (1.0 × 10^9/L) and a single temperature > 38.3 °C or sustained temperature ≥ 38 °C for > 1 hour.

Table 5-10. Platinum Dose Modification Guidelines for Drug-Related Adverse Events

Category	Toxicity	Hold Platinum Treatment for Grade	Timing for Restarting Platinum Treatment	Dose for Restarting Platinum Treatment[a]	Discontinue Platinum
Hematologic	Neutropenia	3[b]	Neutrophil count resolves to ≥ 1000/mm^3 (1.0×10^9/L)	No reduction Consider G-CSF	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded
		4[b]	Neutrophil count resolves to ≥ 1000/mm^3 (1.0×10^9/L)	Reduce by 1 dose level Consider G-CSF	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded
	Thrombocytopenia	2	Platelet count resolves to ≥ 75,000/mm^3 (75×10^9/L) or baseline	No reduction	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded
		3 or 4[b]	Platelet count resolves to ≥ 75,000/mm^3 (75×10^9/L) or baseline	Reduce by 1 dose level	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded
Nonhematologic	Creatinine increased	2 to 4[b]	Toxicity resolves to Grade 0 or 1	For subjects taking carboplatin, reduce by 1 dose level. For subjects taking cisplatin, change cisplatin to carboplatin.	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded
	Ototoxicity or sensory neuropathy	2	May change cisplatin to carboplatin as per local standards May continue treatment with carboplatin as per local standards		
		3 or 4[b]	May switch cisplatin to carboplatin if resolves to ≤ Grade 2 within 12 weeks of last infusion If already using carboplatin, then discontinue		
	All other nonhematologic toxicities[b]	3 or 4[b]	Toxicity resolves to Grade 0 or 1	Reduce by 1 dose level	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded
	Laboratory adverse event[c]	4[b]	Toxicity resolves to ≤ Grade 2	Reduce by 1 dose level	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded

G-CSF = granulocyte colony-stimulating factor

a Restarting platinum should occur on Day 1 of the next cycle after criteria for restarting has been met.

b Permanent discontinuation should be considered for any severe or life-threatening event. Consult the sponsor before restarting treatment after a Grade 4 drug-related adverse event.

c Subjects with an intolerable or persistent Grade 2 drug-related adverse event may hold dosing at the physician's discretion. Permanently discontinue platinum for persistent Grade 2 adverse reactions for which treatment has been held and that do not improve to Grade 0 or 1 within 12 weeks of the last dose. With investigator and sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue in the study only if asymptomatic and the adverse event does not worsen.

5.5.4. 5-Fluorouracil

5-Fluorouracil dose delays and resumption of treatment as well as dose reductions and discontinuation decisions should be conducted in accordance with the current local label and treatment guidelines. General dose modification guidelines for 5-FU for febrile neutropenia or documented infection and drug-related AEs are described in Table 5-11., Table 5-12., and Table 5-13.; these general guidelines may be overridden by local label and/or treatment guidelines with the approval of the medical monitor. If 5-FU is discontinued for reasons other than disease progression, the remaining drug(s) in the combination regimen may be continued.

Table 5-11. 5-Fluorouracil Dose Modification Levels

	Dose Level 0	Dose Level −1	Dose Level −2	Dose Level −3
5-FU	1000 mg/m^2	800 mg/m^2 (20% decrease)	640 mg/m^2 (20% decrease)	Discontinue

5-FU = 5-fluorouracil

Table 5-12. 5-Fluorouracil Dose Modification Guidelines for Febrile Neutropenia or Documented Infection

Adverse Event	Number of Occurrences	Treatment Modification
Febrile neutropenia[a] Documented infection	1	Reduce by 1 dose level The use of growth factors and antibiotics should be considered per local standards
	2	Reduce by 1 dose level Consider prophylactic antibiotics for subsequent cycles The use of growth factors should be strongly considered per local standards
	3	Discontinue 5-FU

5-FU = 5-fluorouracil

a Absolute neutrophil count < 1000/mm^3 (1.0 × 10^9/L) and a single temperature > 38.3 °C or sustained temperature ≥ 38 °C for > 1 hour.

Table 5-13. 5-Fluorouracil Dose Modification Guidelines for Drug-Related Adverse Events

Category	Toxicity	Hold 5-FU Treatment for Grade	Timing for Restarting 5-FU Treatment	Dose for Restarting 5-FU Treatment	Discontinue 5-FU
Hematologic	Neutropenia	3[a]	Neutrophil count resolves to ≥ 1000/mm^3 (1.0×10^9/L)	No reduction Consider G-CSF	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded
		4[a]	Neutrophil count resolves to ≥ 1000/mm^3 (1.0×10^9/L)	Reduce by 1 dose level Consider G-CSF	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded
	Thrombocytopenia	2	Platelet count resolves to ≥ 75,000/mm^3 (75×10^9/L) or baseline	No reduction	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded
		3 or 4[a]	Platelet count resolves to ≥ 75,000/mm^3 (75×10^9/L) or baseline	Reduce by 1 dose level	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded
Nonhematologic	Creatinine increased	2 to 4[a]	Toxicity resolves to Grade 0 or 1	No reduction	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded
	Mucositis diarrhea	2 to 4[a]	Toxicity resolves to Grade 0 or 1	Reduce by 1 dose level	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded
	Hand-foot syndrome	2	Toxicity resolves to Grade 0 or 1	No reduction	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded
		3 to 4[a]	Toxicity resolves to Grade 0 or 1	Reduce by 1 dose level	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded

Category	Toxicity	Hold 5-FU Treatment for Grade	Timing for Restarting 5-FU Treatment	Dose for Restarting 5-FU Treatment	Discontinue 5-FU
	All other nonhematologic toxicities[b]	3 to 4[a]	Toxicity resolves to Grade 0 or 1	Reduce by 1 dose level	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded
	Laboratory adverse event[b]	4[a]	Toxicity resolves to ≤ Grade 2	Reduce by 1 dose level	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded

5-FU = 5-fluorouracil; G-CSF = granulocyte colony-stimulating factor

a Permanent discontinuation should be considered for any severe or life-threatening event. Consult the sponsor before restarting treatment after a Grade 4 drug-related adverse event.

b Subjects with an intolerable or persistent Grade 2 drug-related adverse event may hold dosing at the physician's discretion. Permanently discontinue 5-FU for persistent Grade 2 adverse reactions for which treatment has been held and that do not improve to Grade 0 or 1 within 12 weeks of the last dose. With investigator and sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue in the study only if asymptomatic and the adverse event does not worsen.

5.5.5. Docetaxel

Docetaxel is known to cause neutropenia, hepatotoxicity, peripheral neuropathy, fluid retention, and hypersensitivity reactions. Subjects with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions. Subjects developing peripheral edema may be treated with standard measures (eg, salt restriction, oral diuretics).

Docetaxel dose delays and resumption of treatment as well as dose reductions and treatment discontinuation decisions should be conducted in accordance with the current local docetaxel label and treatment guidelines. The docetaxel dose may not be re-escalated following a dose reduction.

Recommended initial dose and dose reductions for docetaxel:

- Initial dose: 75 mg/m^2
- First dose level reduction: 55 or 60 mg/m^2 (as per local label and guidelines for docetaxel)
- Second dose level reduction: Per investigator's discretion (as per local label and guidelines for docetaxel)

Docetaxel should not be administered to subjects who have significant liver dysfunction or a neutrophil count of less than 1500 cells/mm^3 (refer to local label for liver function requirements for dosage and dose modification for hematologic toxicities).

Subjects who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils less than 500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, or other Grade 3/4 nonhematologic toxicities during docetaxel treatment should have treatment withheld until resolution of the toxicity and then resume dosing at the next dose level reduction.

General criteria for permanent discontinuation of docetaxel:

- Grade 3 or higher peripheral neuropathy
- Cystoid macular edema
- Severe hypersensitivity reaction to docetaxel
- Consider discontinuation for severe cutaneous AEs (eg, Stevens Johnson syndrome)

Docetaxel treatment may be discontinued if there is more than a 5-week dose delay from the last dose or failure to resolve a toxicity within 3 weeks of the last dose of docetaxel.

The general guidelines for dose reductions, holds, and discontinuation may be overridden by local label and/or treatment guidelines with the approval of the medical monitor.

5.6. Prior and Concomitant Medications

5.6.1. Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the local community standards of medical care. Concomitant medications, including all prescription, over-the-counter, herbal supplements, and IV medications and fluids received within 30 days before the first dose of study treatment through the 60-day follow-up visit should be recorded in the electronic case report form (eCRF). If changes occur during the study period, documentation of drug name, indication, route, and date will also be included on the eCRF.

Palliative and supportive care is permitted during the course of the study for underlying medical conditions and management of symptoms.

Surgery purely for tumor control is not permitted during the study. Palliative radiotherapy is permitted to a single lesion if considered medically necessary by the treating physician as long as the lesion is not a RECIST V1.1–defined target lesion. During Part 1 of the study, subjects who tolerate GS-3583 beyond the DLT evaluation period will have the option to receive SBRT starting at Cycle 2 per investigator's discretion. Selection of subject and provision of SBRT will be according to the institution's own protocol and in line with the local standard of care. In subjects receiving radiotherapy, RECIST-designated target lesions will not be subjected to any form of radiotherapy including SBRT. In Part 2 of the study, SBRT is not permitted except after discontinuation of *all* study treatment.

Treatment with GS-3583 may be withheld during the course of palliative radiotherapy or SBRT and should be resumed at the next scheduled administration of study therapy when the investigator deems it is safe to do so. The specifics of the radiation treatment, including the location, will be recorded. Subjects who cannot tolerate GS-3583 following radiotherapy will be discontinued from the study.

5.6.1.1. Rescue Medications and Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered. All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids or rehydration solutions. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

- Anemia: Transfusions may be utilized as clinically indicated for the treatment of anemia but should be clearly noted as concurrent medications or in a transfusion page. Consider a potential immunologic etiology and follow the ASCO guidelines for use of erythropoietin or derivatives.

- Neutropenia: Prophylactic use of colony-stimulating factors including granulocyte colony-stimulating factor (G-CSF), pegylated G-CSF, or granulocyte macrophage colony-stimulating factor (GM-CSF) is not allowed in this study. Therapeutic use of G-CSF and GM-CSF are allowed in subjects with Grade 3 to 4 febrile neutropenia. (**Note**: Administration of GM-CSF might affect pharmacodynamic assessments (peripheral DC count) and therefore must be appropriately documented in the eCRF). Consider a potential immunologic etiology.

- Thrombocytopenia: Transfusion of platelets may be used, if clinically indicated. Immune thrombocytopenia purpura should be ruled out before initiation of platelet transfusion.

- Anti-infectives: Subjects with suspected or documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

- Adverse events with a potential immunologic etiology (irAEs): Follow ASCO or local institutional practice guidelines for identification, evaluation, and management of AEs of a potential immunologic etiology. Depending on the type and severity of an irAE, oral or IV treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition.

5.6.1.2. Stereotactic Body Radiation Therapy (SBRT)

In Part 1 of the study, subjects who tolerate GS-3583 beyond the DLT evaluation period will have the option to receive SBRT starting at Cycle 2 per investigator's discretion. Selection of subject and provision of SBRT will be according to the institution's own protocol and in line with the local standard of care. In subjects receiving SBRT, RECIST-designated target lesions will not be irradiated. SBRT is not permitted during Part 2 of the study except after discontinuation of *all* study treatment.

5.6.2. Prohibited and/or Restricted Treatments

Subjects are prohibited from receiving the following therapies and treatments during the study. Study treatment will be discontinued in subjects who, in the assessment by the investigator, require the use of any of the following therapies and treatments for clinical management:

- Immunotherapy not specified in this protocol
- Chemotherapy
- Investigational agents other than GS-3583 and zimberelimab
- Anticancer biologics
- Corticosteroids are not permitted with the following exceptions:
  - As premedication for known hypersensitivity reactions (eg, IV contrast, IV drug infusion);

    Note: Premedication should not be administered routinely prior to dosing of GS-3583. Refer to Section 5.5.1.3 for subsequent premedication recommendations following GS-3583-related infusion reactions.
  - Intraocular, intranasal, inhaled, and/or topical corticosteroids; and/or
  - Prednisone at doses of up to 10 mg per day or equivalent
  - Required dose and schedule for treatment of irAEs
  - With prior approval from the medical monitor
- Live vaccines within 30 days prior to first dose of study drug through 90 days after the last dose of study drug for anti-PD-1- containing regimens. Administration of the COVID-19 vaccine or inactive influenza vaccinations are permitted (Section 5.7.1).
- Surgery for tumor control

- Any form of radiotherapy for RECIST V1.1–defined target lesion(s)

There are no prohibited therapies during the posttreatment follow-up phase.

5.6.3. Other Restrictions and Precautions

The following nondrug therapies must not be administered or performed during the study:

- Major elective surgery
- Herbal remedies with immunostimulating properties (eg, mistletoe extract) or that are known to potentially interfere with major organ function (eg, hypericin)
- Subjects should not abuse alcohol or other drugs during the study.

In addition to the prohibited medications listed in Section 5.6.2, many herbal and natural remedies have effects on the PK of anticancer medicines and should be discouraged. Specific medications can be discussed with the medical monitor.

5.6.4. Cisplatin, Carboplatin, 5-Fluorouracil, and Docetaxel

Refer to the current local prescribing information for cisplatin, carboplatin, 5-FU, and docetaxel for permitted and prohibited concomitant medications.

Subjects receiving cisplatin may receive pretreatment hydration per local standards and maintain hydration and urinary output for 24 hours after cisplatin administration.

5.6.5. COVID-19 Vaccine and Prophylaxis

There are no substantial safety data regarding the concurrent administration of the COVID-19 vaccine and GS-3583, zimberelimab, cisplatin, carboplatin, 5-FU, or docetaxel. Subjects are allowed to receive the COVID-19 or influenza vaccines to reduce the risk and complications of COVID-19 or influenza infection. The study visits should continue as planned if vaccination occurs while the subject is on the study.

Any immunotherapy for the prophylaxis or prevention of COVID-19 infections may be administered with the approval of the medical monitor but it is not advisable during the DLT evaluation period; subject enrollment into the study should be planned accordingly.

5.7. Accountability for Investigational Medicinal Product

The investigator is responsible for ensuring adequate accountability of all used and unused study drug and vials. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition).

Each study site must keep accountability records that capture:

- The date received and quantity of study drug vials
- The date, subject number, and the study drug kit number dispensed
- The date, quantity of used and unused study drug vials, along with the initials of the person recording the information

5.7.1. Timing of Dose Administration

For safety run-in Cohort A and randomized, disease-specific Cohort A treatment arm, GS-3583 should be administered first before administration of zimberelimab, followed by platinum and 5-FU.

For randomized, disease-specific Cohort A Control Arm, zimberelimab should be administered first, followed by platinum and 5-FU.

For safety run-in Cohort B and randomized, disease-specific Cohort B treatment arm, GS-3583 should be administered first before administration of docetaxel.

There will be a minimum of 1-hour observation period between the completion of GS-3583 infusion and the start of next agent/therapy or their corresponding premedication.

All study drugs may be administered up to 3 days before or after the scheduled dosing date for administrative reasons per the investigator's judgment (up to 5 days after randomization is permitted). Any deviation from this will require agreement with the medical monitor.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons (eg, elective surgery, unrelated medical events, subject vacation, and holidays) not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the subject's study record.

5.7.2. Investigational Medicinal Product Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for electronic master file. If study drug is destroyed at the site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

For both disposal options listed above, the study monitor must first perform drug accountability during an on-site monitoring visit.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject screened or enrolled in the study are presented in tabular form in Appendix 4 and described in the text that follows.

The investigator must document any deviation from the protocol procedures and notify Gilead or the contract/clinical research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment into the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Subjects will be screened within 28 days before enrollment to determine eligibility for participation in the study. The following will be performed and documented at screening:

- Obtain written informed consent
- Review of inclusion/exclusion criteria
- Review of medical history, including smoking status and demographics
- Review of baseline symptoms
- Review of prior and concomitant medications
- Obtain cancer disease details and prior treatments
- Full physical examination including vital signs, body weight, and height
- Perform 12-lead electrocardiogram (ECG)
- Perform ECHO or MUGA scan (results from ECHO or MUGA scan performed up to 30 days prior to enrollment are acceptable)
- Assess ECOG performance status
- Obtain blood samples for:
  - Hematology and serum chemistry

- Serum pregnancy test (females of childbearing potential)
- Coagulation
- Endocrine function
- HIV screening (for subjects with positive result for HIV, a confirmatory test will be conducted)
- HBV, HCV, and HPV serologies
  - For HBV serology, hepatitis B surface antigen, hepatitis B surface antibody, and total anti-HBc. For subjects where total anti-HBc is positive, HBV DNA by quantitative polymerase chain reaction will be required.
  - For HCV serology, HCV antibody. For subjects with positive HCV antibody, HCV RNA by quantitative polymerase chain reaction will be required.
  - In Part 2 Cohort A (HNSCC), subjects with cancer of oropharynx will have HPV testing performed by p16 IHC analysis using locally available validated assay. A central laboratory may be used if testing as specified is not available locally.

    Note: Subjects in Part 2 Cohort A (HNSCC) with oral cavity, hypopharynx, or larynx cancer are not required to undergo HPV testing by p16 IHC as by convention they are assumed to be HPV negative
- Whole blood sample for CHIP mutation analysis
- Whole blood sample for circulating tumor DNA

- Subjects in Part 2 Cohort A (HNSCC) will have baseline CPS using a locally available validated assay
- Obtain urine for urinalysis
- Part 1 and Part 2 Safety Run-in Cohorts: Collection of archival tumor biopsy as FFPE blocks or 10 to 25 unstained slides for analysis of tumor mutations.[redacted]
- Part 2 Randomized Expansion Cohorts: Collection of archival tumor biopsy as FFPE blocks or 10 to 25 unstained slides for analysis of tumor mutations. In addition to the collection of the archival tumor biopsy, each subject enrolled in these cohorts shall undergo a mandatory tumor biopsy if the investigator considers that no undue risk is posed to the subjects due to biopsy related procedures. A recent archival tumor biopsy obtained after the end of the last line of therapy and not older than 6 months may be substituted for the baseline biopsy.

- Part 2 Cohort B (NSCLC) only: Baseline information on PD-L1 expression level at initial diagnosis, EGFR, ALK, ROS1, or any other known actionable genomic alterations using a locally validated test

- Tumor imaging, unless diagnostic quality tumor imaging is available for exams within 28 days prior to the first dose of study treatment

- Record any serious AEs and all AEs related to protocol-mandated procedures occurring after signing of the informed consent form (ICF)

After a subject signs an ICF, the subject will be assigned a unique, sequential subject number. Once a number is assigned, it cannot be reassigned if the original subject is found to be ineligible or withdraws consent.

Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be enrolled/randomized into the study within 28 days after screening. Subjects who do not meet the inclusion and exclusion criteria will be considered screen fails, and their demographic information and reason for screen failure should be documented.

During the screening period, attention must be given to washout periods for prior treatments and prohibited medications.

From the time of obtaining informed consent through the first administration of study drug, record all serious adverse events (SAEs), as well as any AEs related to protocol-mandated procedures on the adverse events eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be considered medical history. See Section 7, Adverse Events and Toxicity Management, for additional details.

6.2.2. Rescreening Criteria

Subjects who do not enroll within 28 days of screening will be screen failed.

Rescreening may be allowed. Subjects who are rescreened after 28 days must be reconsented with a new screening number, and the screening assessments must be repeated. For subjects who are rescreened within 28 days, assessments with results that would exclude the subject will need to be repeated.

6.2.3. Medical History and Baseline Assessments

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions; history of HBV, HCV, and HIV and any condition diagnosed within the prior 10 years that is considered clinically significant by the investigator. Medical history will also include an assessment of smoking history.

Baseline symptoms will be assessed for each subject at screening.

6.2.3.1. Cancer Disease Details and Prior Treatment

Cancer disease history will be recorded separately and not listed as medical history. Current cancer disease details and prior treatment will be obtained for all subjects including:

- Detailed history of the tumor, including histopathological diagnosis, grading, and staging in accordance with the eighth edition of the American Joint Committee on Cancer (AJCC-8) staging manual tumor node metastasis classification at diagnosis
- All therapy used for prior treatment of the tumor (including surgery, radiotherapy, chemotherapy, and immunotherapy)
- Current cancer signs and symptoms, and side effects from current and/or previous anticancer treatments
- Smoking history
- Tumor markers
  - For Part 2 Cohort A (HNSCC), baseline CPS and HPV status as outlined under Section 6.2.1 will be collected
  - For Part 2 Cohort B (NSCLC), PD-L1 expression level at diagnosis, presence/absence of genomic alterations such as EGFR, ROS1, ALK, or any other known actionable genomic alterations will be collected using a locally validated test.

6.3. Randomization

For Part 1, no randomization procedures will be performed.

For Part 2, after the safety run-in, randomization will occur up to 72 hours prior to the first dose of study drug. Please refer to Section 5.1 (Enrollment/Randomization), as needed.

6.4. Treatment Assessments

6.4.1. Baseline/Cycle 1 Day 1 Predose Assessments

The following will be performed and documented prior to study treatment administration:

- Review inclusion and exclusion criteria
- Review baseline symptoms
- Focused physical examination (may be performed within 72 hours prior to the first dose of study treatment)
- Vital signs (temperature, pulse, respiratory rate, and blood pressure)

- Weight
- Standard 12-lead ECG
- Assess ECOG performance status (may be performed within 72 hours prior to the first dose of study treatment)
- Obtain predose blood samples for:
  - Hematology and serum chemistry (may be performed within 72 hours prior to the first dose of study treatment)
  - GS-3583 PK (≤ 30 minutes before start of infusion)
  - GS-3583 immunogenicity assessment (≤ 30 minutes before start of infusion)
  - Zimberelimab PK (≤ 30 minutes before start of infusion) (Part 2 Cohort A)
  - Zimberelimab immunogenicity assessment (≤ 30 minutes before start of infusion) (Part 2 Cohort A)
  - Whole blood for pharmacodynamic biomarkers (PBMC and plasma). The predose sample will be collected any time prior to the start of infusion at the Day 1 visit. An additional set of predose samples should be collected up to 72 hours prior to the Cycle 1 Day 1 visit, if feasible.
  - Whole blood for blood cell count. The predose sample will be collected any time prior to the start of infusion at the Day 1 visit. An additional set of predose samples should be collected up to 72 hours prior to the Cycle 1 Day 1 visit, if feasible.
  - Whole blood for paxgene RNA
  - Serum pharmacodynamics for circulating factors
  - CCI [redacted]
- Obtain predose urine samples for:
  - Urinalysis (may be performed within 72 hours prior to the first dose of study treatment)
  - Urine pregnancy test for females of childbearing potential (may be performed within 72 hours prior to the first dose of study treatment)
- Obtain predose stool sample for microbiome sequencing. Subjects will collect a sample up to 72 hours prior to the study visit and be reminded to bring in the sample upon their arrival to the clinic.
- Review and record all AEs and concomitant medications

Following the completion of the above assessments, the subject will be enrolled and administered study drug.

6.4.2. Cycle 1 Day 1 Postdose Assessments

The following will be performed and documented after administration of study treatment:

- Obtain postdose blood samples for:
  - GS-3583 PK (at end of infusion [+ 5 minutes], 2 hours [± 10 minutes], and 6 hours [± 0.5 hours] after start of infusion) (Part 1 and Part 2 safety run-in Cohort A and B)
  - GS-3583 PK (at end of infusion [+ 5 minutes]) (Part 2 randomized expansion Cohort A and B)
  - Zimberelimab PK (at end of infusion [+ 5 minutes]) (Part 2 Cohort A)
  - Whole blood for CHIP mutation analysis
  - Whole blood for TCR sequencing
  - Whole blood for circulating tumor DNA
- Vital signs (temperature, pulse, respiratory rate, and blood pressure; 1 hour [± 15 minutes] after end of infusion)
- Standard 12-lead ECG (2 hours [-10/+20 minutes] after end of infusion)
- Observation for 1 hour after end of infusion for irAEs

6.4.3. Vital Signs, Weight, and Height

The investigator or qualified designee will take vital signs at screening, prior to, and following the administration of each dose of study treatment, and throughout the study through the follow-up period as specified in the Study Procedures Table (Appendix 4). Vital signs will only be measured while the subject is in a sitting, semirecumbent, or supine position. Vital signs include temperature, pulse, respiratory rate, and blood pressure. Weight should be assessed as specified in Appendix 4 prior to dosing, at the beginning of each cycle, and through the follow-up period. Height will be measured at screening only.

6.4.4. Physical Examination

6.4.4.1. Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the screening period and at the end of treatment visit as specified in the Study Procedures Table (Appendix 4). Clinically significant abnormal findings should be recorded as medical history. After consent, new clinically significant abnormal findings should be recorded as AEs as per Section 7.3.

6.4.4.2. Focused Physical Examination

For cycles that do not require a full physical examination as specified in the Study Procedures Table (Appendix 4), the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to study treatment administration and at the 60-day follow-up. New clinically significant abnormal findings should be recorded as AEs.

6.4.4.3. Eastern Cooperative Oncology Group Performance Status

The ECOG performance status will be assessed at screening, prior to the administration of each dose of study treatment, end of treatment (EOT), and at the 60-day follow-up as specified in Appendix 4.

6.4.5. 12-Lead Electrocardiogram (ECG)

A standard 12-lead ECG will be performed using local standard procedures at screening, prior to the administration, and following the completion of study treatment on Cycle 1 Day 1, after infusion on Cycle 1 Day 15 (Part 1 only), Cycle 2 Day 1, and Day 1 of every odd numbered cycle starting at Cycle 3, the end of treatment visit, and the 60-day follow-up as specified in Appendix 4. Clinically significant abnormal findings at screening should be recorded as medical history.

6.4.6. Echocardiogram (ECHO) or MUGA Scan

A full standard ECHO evaluation will be performed using local standard procedures at screening to establish a baseline. A MUGA scan is also allowed. Results from ECHO or MUGA scan performed up to 30 days prior to enrollment are acceptable for establishing a baseline. Clinically significant abnormal findings at screening should be recorded as medical history and discussed with the medical monitor.

6.4.7. Prior and Concomitant Medications

Prior medication taken by the subject within 30 days prior to screening visit will be recorded. In addition, record all treatments for a prior cancer other than current cancer even if taken greater than 30 days prior to screening. Prior treatments for the current cancer will be recorded separately and not listed as a prior medication.

Concomitant medications, if any, taken by the subject during the study from the date of consent through the 60-day follow-up visit will be recorded. After the 60-day follow-up visit, all medications related to reportable SAEs will be recorded as defined in Section 7.3.3.

6.4.8. Clinical Laboratory Assessments

The central laboratory will be responsible for chemistry, hematology, coagulation, endocrine function, urinalysis, HIV, HBV and HCV serology, and serum pregnancy testing as well as processing and/or storage of other study samples. Specific instructions for processing, labeling, and shipping samples will be provided in a central laboratory manual. The date and time of sample collection will be reported to the central laboratory.

If central laboratory results are not available, local laboratories may be used for dosing decisions. Local laboratory assessments resulting in a dose change or as part of an AE assessment, which is not supported by central laboratory results, will be reported on the eCRF. Gilead's standard reference ranges will be used.

Urine pregnancy tests will be performed locally at the site as shown in Appendix 4.

- For Part 1, following the 60-day follow-up visit, urine pregnancy tests will be performed monthly until 12 weeks after the last dose of study drug.

- For Part 2, following the 60-day follow-up visit, urine pregnancy tests will be performed monthly until the end of the contraception requirement (Appendix 5).

Laboratory tests for screening should be performed within 28 days prior to the first dose of study treatment. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to the first dose of study treatment. The report of the results must be retained as a part of the subject's medical record or source documents. Blood samples for study-related tests will be collected at time points specified in Appendix 4.

Table 6-1. Analytes

Chemistry	Urinalysis	Hematology	Other
Albumin Alkaline phosphatase ALT AST Bicarbonate BUN/total urea Calcium Chloride Serum creatinine[a] CRP GGT Glucose LDH Lipase Cholesterol Triglycerides Amylase Magnesium Phosphorus/phosphates Potassium Sodium Total bilirubin Direct bilirubin Total protein Uric acid	Color and appearance Specific gravity pH Occult blood Protein Glucose Bilirubin Leukocyte esterase Nitrite Urobilinogen Ketones Microscopic	WBC and differential absolute count Basophils Eosinophils Lymphocytes Monocytes Neutrophils ANC Hemoglobin Hematocrit Platelet count MCV RBC **Coagulation** Prothrombin time INR aPTT	Serum β-hCG or urine pregnancy test[c] FSH (reflex) Endocrine Function Tests (TSH and free T4[d]) Basal cortisol HIV HBV and HCV Serology[b] **Screening only:** **Part 2 Cohort A (HNSCC):** HPV p16 expression testing as indicated CPS **Part 2 Cohort B (NSCLC):** PD-L1 expression at diagnosis and other tumor markers per Section 6.2.1.

β-hCG = beta-human chorionic gonadotropin; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; CPS = combined positive score; FSH = follicle stimulating hormone; GGT = gamma-glutamyltransferase; HBV = hepatitis C virus; HCV = hepatitis C virus; HNSCC = head and neck squamous cell carcinoma; INR = international normalized ratio; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; NSCLC = National Comprehensive Cancer Network; RBC = red blood cell; T4 = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell

a Estimated creatinine clearance (CL_{cr})/glomerular filtration rate will be calculated based on the Cockcroft-Gault formula using actual body weight: CL_{cr} (mL/min) = (140 − age [years])* weight (kg)/(serum creatinine [mg/dL]*72). If the subject is female, multiply the quantity by 0.85.

b For HBV serology, hepatitis B surface antigen, hepatitis B surface antibody, and total antibody against hepatitis B core antigen (anti-HBc). For subjects where total anti-HBc is positive, HBV DNA by quantitative polymerase chain reaction will be required.
For HCV serology, HCV antibody. For subjects with positive HCV antibody, HCV RNA by quantitative polymerase chain reaction will be required.

c Females of childbearing potential only. Serum pregnancy will be conducted at screening and urine pregnancy test at all other indicated visits.

d T4 will be tested reflexively based on abnormal TSH results.

6.4.9. Tumor Biopsies

Part 1: Tumor tissue for biomarker analysis will be collected at the time of screening from an archival tumor biopsy, obtained preferably either at the time of or after the diagnosis of advanced disease has been made, and from a site not previously irradiated.

If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred that a new baseline scan be obtained.

CCI [redacted]

CCI [redacted]

[redacted]

Part 2:

Baseline: Tumor tissue for analysis of tumor mutations will be collected at the time of screening from an archival tumor biopsy, obtained preferably either at the time of or after the diagnosis of advanced disease has been made (HNSCC), or after the subject has progressed on the last treatment (NSCLC), and from a site not previously irradiated. This tumor biopsy will be used to analyze changes in the tumor DNA that can be used to track tumor DNA in circulation.

In addition to the archival tumor biopsy, a mandatory fresh tumor biopsy will be collected at baseline from subjects in the randomized expansion cohorts if clinically feasible and if, in the opinion of the investigator, collection poses no undue risk to the subject. This biopsy will be used together with additional on-treatment biopsies to look for changes in the tumor caused by the treatment, and for that reason, a fresh pretreatment biopsy is preferred. While a fresh baseline biopsy is optimal to study treatment effects, a recent archival tissue biopsy (a block, so fresh slides can be cut) obtained after the last line of therapy and not older than 6 months may be substituted for the fresh pretreatment biopsy.

If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred that a new baseline scan be obtained.

On treatment: A mandatory fresh tumor on-treatment biopsy will be collected from subjects in the randomized expansion cohorts any time after Day 15 of Cycle 2, but strongly preferred between Day 15 of Cycles 2 and 4 after completion of radiographic imaging if clinically feasible and if it poses no undue risk to the subject in the judgment of the investigator. This biopsy should ideally be taken from the same metastatic site as the baseline biopsy. CCI [redacted]

Fresh on-treatment and EOT (progressive disease) tumor biopsies will only be collected if a fresh pretreatment tumor biopsy or a recent archival tumor biopsy was collected.

An overview of tumor biopsy requirements in Part 2 is provided in Table 6-2. For additional details and instructions regarding tissue requirements, collection, storage, and shipment, refer to the study laboratory manual.

Table 6-2. Part 2 Tumor Biopsy Collection

	Safety Run-in Cohorts	Randomized Expansion Cohorts
Archival tumor biopsy	Obtain block, or collect 10 to 25 slides (archival tumor biopsy can be replaced with fresh pretreatment biopsy)	Obtain block, or collect 10 to 25 slides
Mandatory fresh pretreatment biopsy	—	Collect (can be replaced with recent archival tumor biopsy not older than 6 month and obtained after the last line of treatment)
Mandatory on-treatment biopsy	—	Collect any time after Day 15 of Cycle 2 (only if fresh pretreatment biopsy was collected)
CCI		

EOT = end of treatment

6.4.10. Testing for HPV Status

In Part 2 Cohort A (HNSCC), subjects with oropharynx cancer must have local assessment of HPV status, defined as p16 IHC testing using a locally available validated test, from tumor tissue prior to randomization.

Note: Subjects with oral cavity, hypopharynx, or larynx cancer are not required to undergo HPV testing by p16 IHC as by convention they are assumed to be HPV negative.

6.5. Pharmacokinetic, Biomarker, and Immunogenicity Assessments

6.5.1. Pharmacokinetic Assessments

6.5.1.1. Pharmacokinetic Parameters

GS-3583 concentrations will be determined by a validated method. The PK parameters to be estimated and reported may include, but may not be limited to, C_{max}, AUC_{tau}, C_{trough}, T_{max}, and CL. Unresolved missing data may be imputed when analysis integrity is affected. The conservative principle will be used for data imputation. Noncompartmental analysis will be used to characterize the PK. Compartmental modeling (eg, population PK) analysis may be conducted.

6.5.1.2. PK Sample Collection

Blood sample collection for GS-3583 PK characterization will be conducted throughout the study. The time for collection of PK blood draws should always be referenced from the start of the infusion. It is important to record all infusion start dates/times, infusion end dates/times, infusion interruption(s) start and end dates/times, infusion flush end dates/times, and blood sample collection dates/times completely and accurately (and to the nearest minute).

Part 1: At Cycles 1 and 3, blood will be collected at predose (≤ 30 minutes before start of infusion), end of infusion (+ 5 minutes), and 2 hours (± 10 minutes), 6 hours (± 0.5 hours), Day 2 (24 hours [± 2 hours]), Day 3 (48 hours [± 4 hours]), Day 5 (96 hours [± 4 hours]), Day 8 (168 hours [± 12 hours]), Day 15 (for Cycle 1: pre-Day 15 dose [≤ 30 minutes before start of infusion], end of Day 15 infusion (+ 5 minutes), and 2 hours after start of Day 15 infusion (± 10 minutes); for Cycle 3: 336 hours [± 12 hours]), and Day 24 (552 hours [± 12 hours]) after start of the Day 1 infusion (Table 6-3).

In addition, samples will be collected on Day 1 (predose), and Day 15 (336 hours) of Cycles 2, 4, and every subsequent even numbered cycle thereafter, and at the 60-day follow-up visit (approximately 60 days after last dose). An additional blood sample will be collected at the EOT visit if a subject terminates early from study treatment.

Table 6-3. Part 1: Schedule of Intensive Pharmacokinetic Assessments

	Day 1	Day 2 (24 h)	Day 3 (48 h)	Day 5 (96 h)	Day 8 (168 h)	Day 15 (336 h)	Day 24 (552 h)
Cycles 1 and 3	Predose, end of infusion, 2 and 6 hours after start of infusion	X	X	X	X	Predose, end of infusion, and 2 hours after start of infusion*	X
Cycles 2, 4, and every subsequent even cycle	Predose	—	—	—	—	X	—
60-Day Follow-up Visit (60 days after last dose)	X	—	—	—	—	—	—
End of Treatment (if subject terminates early)	X	—	—	—	—	—	—

* For Cycle 1: pre-Day 15 dose, end of Day 15 infusion, and 2 hours after start of Day 15 infusion; for Cycle 3: 336 hours.

Part 2 Cohorts A and B

GS-3583 (Safety Run-in Cohorts): At Cycles 1 and 3, blood samples will be collected at predose (≤ 30 minutes before start of infusion), end of infusion (+ 5 minutes), and 2 hours (± 10 minutes), 6 hours (± 0.5 hours), Day 8 (168 hours [± 12 hours]), and Day 15 (336 hours [± 12 hours]) after start of the Day 1 infusion.

In addition, blood samples will be collected on Day 1 (predose [≤ 30 minutes before start of infusion] and end of infusion [+ 5 minutes]) of Cycles 2, 5, and every subsequent odd numbered cycle thereafter, and at the 60-day follow-up visit (approximately 60 days after last dose). An additional blood sample will be collected at the EOT visit if a subject terminates early from study treatment (Table 6-4).

GS-3583 (Randomized Expansion Cohorts Treatment Arms): Blood samples will be collected on Day 1 (predose [≤ 30 minutes before start of infusion] and end of infusion [+ 5 minutes]) of Cycles 1, 2, 3, and every subsequent odd numbered cycle thereafter, and at the 60-day follow-up visit (approximately 60 days after last dose). An additional blood sample will be collected at the EOT visit if a subject terminates early from study treatment.

Part 2 Cohort A

Zimberelimab (Safety Run-in Cohort and Randomized Expansion Cohort Control and Treatment Arms): Blood samples will be collected on Day 1 (predose [≤ 30 minutes before start of infusion] and end of infusion [+ 5 minutes]) of Cycles 1, 2, 3, and every subsequent odd numbered cycle thereafter, and at the 60-day follow-up visit (approximately 60 days after last dose). An additional blood sample will be collected at the EOT visit if a subject terminates early from study treatment (Table 6-4).

Table 6-4. Schedule of GS-3583 Pharmacokinetic Sample Collection for Part 2 Cohort A and B (Safety Run-in and Randomized Expansion Cohorts [Treatment Arms])

Safety Run-in Cohorts A and B				
Sample for	**Visit/Cycle**	**Day 1**	**Day 8 (168 h)**	**Day 15 (336 h)**
GS-3583	Cycles 1 and 3	Predose, end of infusion, 2 and 6 hours after start of infusion	X	X
	Cycles 2, 5, and every subsequent odd cycle (ie, Cycles 7, 9, etc)	Predose and end of infusion	—	—
	60-Day Follow-up Visit (60 days after last dose)	X	—	—

Safety Run-in Cohorts A and B				
Sample for	**Visit/Cycle**	**Day 1**	**Day 8 (168 h)**	**Day 15 (336 h)**
	End of Treatment (if subject terminates early)	X	—	—
Randomized Expansion Cohorts A and B				
Sample for	**Visit/Cycle**	**Day 1**	**Day 8 (168 h)**	**Day 15 (336 h)**
GS-3583	Cycles 1, 2, 3, and every subsequent odd cycle (ie, Cycles 5, 7, etc)	Predose and end of infusion	—	—
	60-Day Follow-up Visit (60 days after last dose)	X	—	—
	End of Treatment (if subject terminates early)	X	—	—

Table 6-5. Schedule of Zimberelimab Pharmacokinetic Sample Collection for Part 2 Cohort A (Safety Run-in and Randomized Expansion Cohorts [Control and Treatment Arms])

Sample for	Visit/Cycle	Day 1
Zimberelimab	Cycles 1, 2, 3, and every subsequent odd cycle (ie, Cycles 5, 7, etc)	Predose and end of infusion
	60-Day Follow-up Visit (60 days after last dose)	X
	End of Treatment (if subject terminates early)	X

6.5.2. Biomarker Assessments

6.5.2.1. Biomarker Sample Collection

Blood samples will be collected from all subjects in the study to assess pharmacodynamic responses, immunological response to GS-3583, and correlates of clinical efficacy and/or safety. Samples will include:

Part 1:

- **Whole Blood for Pharmacodynamic Biomarkers (PBMC and plasma):**

  — Day 1 of Cycle 1 and Cycle 3 at predose, Day 8 (168 hours [± 12 hours]), Day 15 (336 hours [± 12 hours], must be collected predose at Cycle 1), and Day 24 (552 hours [± 12 hours]) after start of the Day 1 infusion. The predose samples will be collected any time prior to the start of infusion at the Day 1 visit. However, for Cycle 1 Day 1, an additional set of predose samples should be collected up to 72 hours prior to the Cycle 1 Day 1 visit, if feasible.

  — Predose on Day 1, and Day 15 (336 hours [± 12 hours]) after start of the Day 1 infusion of Cycles 2, 4, and every subsequent even numbered cycle thereafter

  — End of treatment (for subjects that terminate early from study treatment only)

  — Sixty-day follow-up visit (approximately 60 days after last dose)

  — Two 10 mL samples will be collected at all time points except on Days 8 and 24 in Cycles 1 and 3, when only 1 sample of 10 mL will be collected.

- **Whole Blood for Blood Cell Count:** at the same time points as the Pharmacodynamic Biomarkers (PBMC and plasma) samples above

- **Whole Blood sample for CHIP mutation analysis:** at Screening; anytime on Day 1 of Cycles 1, 2, 3, and every subsequent even cycle; and EOT

- **Whole Blood sample for TCR sequencing:** anytime on Day 1 of Cycles 1, 2, 3, and every subsequent even numbered cycle; and EOT

- **Whole Blood for assessing Circulating Tumor DNA:** at Screening; anytime on Day 1 of Cycles 1, 2, 3, and every subsequent even cycle; and EOT

- **Whole Blood Paxgene RNA:** at predose on Day 1 and Day 15 of Cycle 1, predose on Day 1 of Cycle 2, predose on Day 1 of Cycle 3, any time on Day 15 of Cycle 3, and predose on Day 1 at every subsequent even numbered cycle; and EOT

- **Serum Pharmacodynamics for Circulating Factors:** at predose on Day 1 of Cycles 1, 2, and 3; at predose on Day 15 of Cycle 1; any time on Day 8 of Cycle 1; any time on Days 8 and 15 of Cycle 3; any time on Day 24 of Cycle 1; and EOT

- **Stool Sample for Microbiome Sequencing:** at predose on Day 1 of Cycles 1 and 3, and EOT. Subjects will collect a sample up to 72 hours prior to the study visit and be reminded to bring in the sample upon their arrival to the clinic.

- CCI [redacted]
- **Archival tumor tissue biopsy** collected at screening for evaluation of tumor mutations, if available.
- CCI [redacted]

Part 2:

Safety Run-in Cohorts:

- **Whole Blood for Pharmacodynamic Biomarkers (PBMC and plasma):**
  - Predose at Day 1, and on Day 12 (264 hours [± 12 hours]), and Day 15 (336 hours [± 12 hours]) after start of the Day 1 infusion in Cycles 1 and 3. In Cycle 1 and Cycle 3, the predose samples will be collected any time prior to the start of infusion at the Day 1 visit. However, for Cycle 1 Day 1, additional set of predose samples should be collected up to 72 hours prior to the Cycle 1 Day 1 visit, if feasible.
  - Predose on Day 1 and Day 15 (336 hours [± 12 hours]) after start of the Day 1 infusion of Cycles 2, 4, and every subsequent even numbered cycle thereafter
  - End of treatment (for subjects that terminate early from study treatment only)
  - Sixty-day follow-up visit (approximately 60 days after last dose)
  - Two 10 mL samples will be collected at all time points except on Day 12 in Cycles 1 and 3, when only 1 sample of 10 mL will be collected.

- **Whole Blood for Blood Cell Count:** at the same time points as the Pharmacodynamic Biomarkers (PBMC and plasma) samples above

Randomized Expansion Cohorts:

- **Whole Blood for Pharmacodynamic Biomarkers (PBMC and plasma):**
  - Predose on Day 1 and on Day 15 (336 hours [± 12 hours]) after start of the Day 1 infusion of Cycles 1, 2, 3, 4, and every subsequent even numbered cycle thereafter. However, for Cycle 1 Day 1, an additional set of predose samples should be collected up to 72 hours prior to the Cycle 1 Day 1 visit, if feasible.
  - End of treatment (for subjects that terminate early from study treatment only)
  - Sixty-day follow-up visit (approximately 60 days after last dose)
  - Two 10 mL samples will be collected at all time points.
- **Whole Blood for Blood Cell Count:** at the same time points as the Pharmacodynamic Biomarkers (PBMC and plasma) samples above
- CCI [redacted]

Safety Run-in and Randomized Expansion Cohorts:

- **Whole Blood sample for CHIP mutation analysis:** at Screening; anytime on Day 1 of Cycles 1, 2, 3, and every subsequent even cycle; and EOT
- **Whole Blood sample for TCR sequencing:** anytime on Day 1 of Cycles 1, 2, 3, and every subsequent even numbered cycle; and EOT

- **Whole Blood for assessing Circulating Tumor DNA:** at Screening; anytime on Day 1 of Cycles 1, 2, 3, and every subsequent even cycle; and EOT

- **Whole Blood Paxgene RNA:** at predose on Day 1, and any time of the day on Day 15 of Cycle 1, predose on Day 1 of Cycle 2, predose on Day 1 of Cycle 3, any time on Day 15 of Cycle 3, and predose on Day 1 at every subsequent even numbered cycle; and EOT

- **Serum Pharmacodynamics for Circulating Factors:** at predose on Day 1 of Cycles 1, 2 and 3; any time of the day on Day 15 of Cycles 1 and 3; and EOT

- **Stool Sample for Microbiome Sequencing:** at predose on Day 1 of Cycles 1 and 3, and EOT. Subjects will collect a sample up to 72 hours prior to the study visit and be reminded to bring in the sample upon their arrival to the clinic.

- CCI [redacted]

- **Archival tumor tissue biopsy** collected at screening for evaluation of tumor mutations, if available. If archival tumor tissue is not available, collection of fresh biopsy material can be substituted.

For additional details and instructions regarding tissue requirements, collection, storage, and shipment, refer to the laboratory manual.

6.5.3. Immunogenicity Assessments

The immunogenicity assessments will be conducted to detect and measure ADA against GS-3583 and zimberelimab.

Part 1: Subjects will have ADA assessed at predose (≤ 30 minutes before start of infusion) on Day 1 of Cycle 1, 2, 3, 4, 7, and 13; and at 60-day follow-up visit (approximately 60 days after last dose). An additional blood sample will be collected at the EOT visit if a subject terminates early from study treatment.

Part 2: Safety Run-in Cohorts and Randomized Expansion Cohorts Treatment Arms

GS-3583: Subjects will have ADA assessed at predose (≤ 30 minutes before start of infusion) on Day 1 of Cycle 1, 2, 3, 5, 9, and 17; and at the 60-day follow-up visit (approximately 60 days after last dose). An additional blood sample will be collected at the EOT visit if a subject terminates early from study treatment.

Part 2: Cohort A (Safety Run-in Cohort and Randomized Expansion Cohort: Control and Treatment Arms)

Zimberelimab: Subjects will have ADA assessed at predose (≤ 30 minutes before start of infusion) on Day 1 of Cycle 1, 2, 3, 5, 9, and 17; and at 60-day follow-up visit (60 days after last dose). An additional blood sample will be collected at the EOT visit if a subject terminates early from study treatment.

6.6. Efficacy Assessments

6.6.1. Response Assessment

Response assessment will be performed according to RECIST V1.1 {Eisenhauer 2009}.

For all subjects, tumor response assessment will be performed by computed tomography (CT) scan with contrast or magnetic resonance imaging (MRI) of the chest/abdomen/pelvis (plus other regions as required for specific tumor types). All scans performed at baseline and other imaging performed as clinically required (other supportive imaging) will be repeated at subsequent visits. In general, lesions detected at baseline should be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

For each subject, the investigator will designate 1 or more of the following measures of tumor status to follow for determining response: CT or MRI images of primary and/or metastatic tumor masses, physical examination findings, and results of other assessments. All available images collected during the study period will be considered. The most appropriate measures to evaluate a subject's tumor status should be used. Measure(s) chosen for sequential evaluation during the study must correspond to measures used to document progressive tumor status that qualifies the subject for enrollment.

Subjects who experience initial radiologic progressive disease and are doing well clinically are considered to have initial RECIST V1.1-defined progressive disease and will be permitted, with Gilead's approval, to continue with study drug treatment (see Section 3.4.1). These subjects will be reevaluated using the same imaging modality no less than 4 weeks later (after the last imaging with initial RECIST V1.1-defined progressive disease) to assess whether study drug treatment will be continued. If initial progression is based on occurrence of a new lesion in an area not scanned at baseline, an on-study scan no less than 4 weeks from initial observation of new lesion should be considered before performing the EOT visit.

Tumor responses to treatment will be assigned based on evaluation of response of target, nontarget, and new lesions according to RECIST V1.1 (all measurements should be recorded in metric notation; see {Eisenhauer 2009}). To assess objective response, tumor burden at baseline will be estimated and used for comparison with subsequent measurements. At baseline, tumor lesions will be categorized in target and nontarget lesions as described in {Eisenhauer 2009}.

Results for these evaluations will be recorded with as much specificity as possible so that pretreatment and posttreatment results will provide the best opportunity for evaluating tumor response.

Any complete response (CR) or partial response (PR) should be confirmed by CT or MRI scan as described in {Eisenhauer 2009} no less than 4 weeks after initial assessment. The confirmatory scan may replace the next scheduled scan.

The investigator may perform scans in addition to a scheduled study scan for medical reasons or if progressive disease is suspected.

Part 1: Subjects who may receive SBRT at investigator's decision will not have their designated target lesion (per RECIST V1.1) subjected to SBRT.

Part 2: SBRT is not permitted, except after discontinuation of *all* study treatment.

6.6.2. Tumor Assessments

6.6.2.1. Tumor Imaging

Investigator-assessed imaging will be performed at defined time points. The initial tumor imaging to establish baseline disease will be performed ≤ 28 days prior to first dose of study drug. Scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and ≤ 28 days prior to first dose of study drug. On-study imaging as listed in Table 6-6 will be performed as specified below and in Appendix 4.

Table 6-6. Postbaseline Imaging Schedule

Cohort	Postbaseline Imaging Schedule	Duration of Tumor Imaging Assessments
Part 1	Every 8 weeks from the first treatment dose (Visit window ± 7 days)	Until progressive disease is assessed by investigator, new line of anticancer therapy, or 1 year after last treatment dose, whichever occurs first
Part 2 (Cohorts A and B)	Every 6 weeks from the first treatment dose (Visit window ± 7 days) until Week 24, then every 9 weeks thereafter starting at Week 33[a]	Until progressive disease is assessed by investigator, new line of anticancer therapy, or 1 year after last treatment dose, whichever occurs first

Per RECIST V1.1, PR or CR should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. The scan for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (ie, 6 weeks later), whichever is clinically indicated.

The timing of on-study treatment imaging should follow study calendar days starting from Cycle 1 Day 1 and should not be adjusted for delays in treatment administration or for visits. The same imaging technique should be used in a subject throughout the study. Tumor imaging may be performed by CT or MRI. CT scan is the more commonly used modality and is preferred for the majority of subjects. An MRI can be utilized if clinically appropriate. Imaging should include the head, neck, chest, abdomen, and pelvis. In general, lesions detected at baseline should be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits. The investigator may perform scans in addition to a scheduled study scan for medical reasons or if progressive disease is suspected.

For subjects who permanently discontinued all study drug(s) in the absence of progressive disease (eg, experienced unexpected toxicity) and/or start of new anticancer therapy, CT or MRI imaging should continue to be performed at the predefined schedule, until documented progressive disease, initiation of a new anticancer therapy other than the study treatment, or up to 1 year after the last dose of study drug, whichever occurs first (see Section 6.8.1.1); and then move into survival follow-up for up to 1 year after the completion/discontinuation of tumor lesion assessments.

For subjects who permanently discontinue from the study in the absence of progressive disease/or start of a new line of anticancer therapy and will not be continuing tumor imaging during the posttreatment period (ie, withdrew consent), additional imaging is recommended at the EOT visit if the last imaging was performed more than 30 days prior.

For subjects that met progressive disease clinically, subjects will continue tumor imaging until progressive disease is confirmed radiographically or prior to the start of a new line of anticancer therapy. As outlined in Section 3.4.1, subjects who experience initial radiologic progressive disease but improve clinically are considered to have initial RECIST V1.1-defined progressive disease and will be permitted, with Gilead's approval, to continue with study drug treatment(s). These subjects will be reevaluated using the same imaging modality no less than 4 weeks later (after the last imaging with initial RECIST V1.1-defined progressive disease) to assess whether study drug treatment will be continued.

6.7. Sample Storage

The stored biological samples may be used by Gilead or its research partner for future testing to provide additional data to answer questions that relate to the main study. At the end of this study, these samples may be retained in storage by Gilead for a period up to 15 years. If subjects provide additional specific consent, residual PK samples may be destroyed no later than 15 years after the end of study or per country requirements.

6.8. Unscheduled Visits

Unscheduled visits may occur at any time while the subject is enrolled on study. Data generated during an unscheduled visit will be collected in subject source documents and captured in the eCRFs. Multiple visits occurring during the 28-day screening period are not considered unscheduled and all data related should be captured in the screening eCRF.

6.8.1. End of Treatment and Posttreatment Visits

6.8.1.1. End of Treatment Visit

The end of treatment (EOT) visit (refer to Appendix 4, Study Procedures Tables) should occur at the time when study drug is permanently discontinued for any reason. If the EOT visit occurs 60 days from the last dose of study treatment, at the time of the 60-day follow-up visit, then the same assessments can be done once and reported under both EOT and 60-day follow-up visits. Subjects that terminate early from study treatment will have blood samples collected for PK, pharmacodynamic, and immunogenicity assessments at the EOT visit.

Subjects who discontinue from study treatment for reasons other than progressive disease will continue to have tumor imaging at the predefined schedule, until documented progressive disease, initiation of a new anticancer treatment, or up to 1 year after the last dose of study drug, whichever occurs first (refer to Section 6.6.2.1); and then move into survival follow-up for up to 1 year. If that is not feasible or acceptable to the subject (ie, subject withdrew consent) additional imaging is recommended at the EOT visit if the last imaging was performed more than 30 days prior.

6.8.1.2. Sixty-Day Follow-up Visit

The 60-day follow-up visit (refer to Appendix 4, Study Procedures Tables) will be conducted for all subjects approximately 60 (± 7) days after the last dose of study treatment or before the initiation of a new anticancer treatment, whichever comes first. Subjects with an AE of Grade > 1 will be further followed until the resolution of the AE to Grade 0 or 1 or until initiation of a new anticancer therapy, whichever occurs first.

For all females of childbearing potential in Part 1, urine pregnancy tests will be performed monthly until 12 weeks after the last dose of study drug.

For all females of childbearing potential in Part 2, urine pregnancy tests will be performed monthly until the end of the contraception requirement (Appendix 5).

6.8.2. Survival Follow-Up

After the posttreatment 60-day follow-up visit, subjects who present(ed) with progressive disease and/or start(ed) a new anticancer therapy will move into survival follow-up. During the survival follow-up period, subjects will be contacted by telephone to assess for survival status and any new malignancies every 3 months for up to 1 year. No imaging assessment is required for survival follow-up. Information about deaths solicited during the survival follow-up period should be reported, but will not be considered or reported as SAEs except as those events described in Section 7.1.2.2 and 7.3.3. Investigators should abide by the reporting obligations as stated in Section 7.

Subjects who do not present with progressive disease and/or start a new anticancer therapy will continue tumor imaging assessments until documented progressive disease, initiation of a new anticancer therapy, or up to 1 year after the last dose of study drug, whichever occurs first; and then move into the survival follow-up period for up to 1 year.

6.9. Poststudy Care

Upon withdrawal from study and/or completion of the survival follow-up period, subjects will receive the care which they and their physician(s) (investigators) agree upon.

6.10. Assessments for Early Discontinuation from Study Treatment or Study

If a subject discontinues study dosing (eg, as a result of an AE or other reasons listed in Section 6.10.1, Criteria for Discontinuation of Study Treatment), the EOT (Section 6.8.1.1), 60-day follow-up (Section 6.8.1.2), and survival follow-up visits (Section 6.8.2) will be performed, and every attempt should be made to keep the subject in the study to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

Subjects that terminate early from study treatment will have blood samples collected for PK, pharmacodynamic, and immunogenicity assessments at the EOT visit. For subjects who permanently discontinue from the study in the absence of progressive disease/or start of a new line of anticancer therapy and will not be continuing tumor imaging during the posttreatment period, additional imaging is recommended at the visit if the last imaging was performed more than 30 days prior.

6.10.1. Criteria for Discontinuation of Study Treatment

Study drug may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Unacceptable toxicity per ASCO Toxicity Guidelines (Appendix 3), or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the subject's best interest
- Progressive disease
- Initiation of a new anticancer therapy
- Death
- Lost to follow-up
- Subject request to discontinue for any reason

- Investigator's discretion
- Protocol violation or major protocol deviation
- Pregnancy during the study (Appendix 5)
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an IRB or IEC

6.11. End of Study

End of study will be defined as when the last subject reaches the last scheduled follow-up time point (including the 60-day follow-up or survival follow-up, whichever occurs the latest), or lost to follow-up, withdraws from the study, death, or the time at which Gilead closes the study.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a study drug, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.3).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social, and/or convenience admissions)
- Overdose without clinical sequelae (Section 7.1.3)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented as medical history.
- Disease progression due to underlying disease

Preexisting events that increase in severity or change in nature after study drug initiation or during or as a consequence of participation in the clinical study will be considered AEs.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death
- A life-threatening situation (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)

- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: Such events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.1.2.1. Protocol-Specific Serious Adverse Event Definitions

In order to maintain the integrity of the study, the following events that are assessed as unrelated to study drugs will not be considered SAEs:

- Disease progression due to underlying disease
- Death from disease progression due to underlying disease

Disease progression and death from disease progression should be reported as SAEs by the investigator, only if it is assessed that the study drug caused or contributed to the disease.

All new malignancies, other than which was being studied during treatment with GS-3583, that occur during the study or the posttreatment/survival follow-up period up to 1 year after the completion/discontinuation of lesion tumor assessments will be deemed medically important and reported as an SAE.

7.1.2.2. Adverse Events of Special Interest

- All new malignancies, other than which was being studied during treatment with GS-3583, that occur during the study or the posttreatment/survival follow-up period will be deemed medically important and reported as an SAE.
- Following the completion/discontinuation of tumor lesion assessments per the tumor imaging schedule outlined in section 6.6.2.1 (as applicable), subjects will be contacted by telephone every 3 months for up to 1 year during the survival follow-up period to determine if any new malignancies have developed since their last dose of GS-3583.

7.1.3. Study Drugs and Gilead Concomitant Therapy Special Situations Reports

Special situation reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration, or administration of a study drug while the medication is in the control of a healthcare professional, subject, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a subject.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead study drug.

Counterfeit or falsified medicine: Any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).
- **Yes**: There is reasonable possibility that the AE may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of protocol procedures (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the NCI CTCAE toxicity grading scale, Version 5.0. For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale (Appendix 6).

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study medication, the following types of events must be reported on the applicable eCRFs: all SAEs and AEs related to protocol-mandated procedures.

7.3.2. Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 60 days (for Part 1) or 90 days (for Part 2) after the last administration of study drug or start of subsequent therapy, whichever occurs first and report them on the eCRFs as instructed.

All AEs and clinically significant laboratory abnormalities should be followed until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the subject first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the 60 days (for Part 1) or 90 days (for Part 2) after the last dose of study drug, must be reported on the applicable eCRFs and GLPS (formerly Gilead Pharmacovigilance and Epidemiology) as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the informed consent form is signed.

Any SAEs and deaths that occur within 90 days of the last dose of study drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after 60 days (for Part 1) or 90 days (for Part 2) after the last dose of study drug; however, if the investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to Gilead GLPS.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the posttreatment follow-up, must be reported to Gilead GLPS (Section 7.4.2). Adverse events and SAEs resulting from SSRs must be reported in accordance with the AE and SAE reporting guidance (Section 7.3).

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situation reports involving a Gilead concomitant therapy (not considered study drug), that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including 60 days (for Part 1) or 90 days (for Part 2) after the last dose of study drug, must be reported to Gilead GLPS utilizing the paper SSR (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Therapy Report

Special situations involving non-Gilead concomitant medications does not need to be reported on the SSR form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situation Reports

7.4.1. Serious Adverse Event Reporting Process

For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

Additional information may be requested to ensure the timely completion of accurate safety reports.

Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the SAE narrative section of the safety report form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

Site personnel will record all SAE data on the applicable eCRFs and from there transmit the SAE information to Gilead GLPS within 24 hours of the investigator's knowledge of the event from ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

If it is not possible to record and transmit the SAE information electronically, record the SAE on the paper SAE reporting form and transmit within 24 hours:

Gilead GLPS:	Gilead GLPS Email: PPD or Fax: PPD

If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to Gilead GLPS.

7.4.2. Special Situations Reporting Process

7.4.2.1. Paper Special Situations Reporting Process for Study Drugs

All SSRs will be recorded on the SSR form and transmitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead GLPS from study drugs' initiation throughout the duration of the study, including the protocol required posttreatment follow-up period.

Gilead GLPS: Gilead GLPS
Email: PPD
or
Fax: PPD

7.4.2.2. Reporting Process for Gilead Concomitant Medications

Special situations that involve Gilead concomitant medications that are not considered study drugs must be reported within 24 hours of the investigator's knowledge of the event to Gilead GLPS utilizing the paper special situations report form to:

Gilead GLPS: Gilead GLPS
Email: PPD
or
Fax: PPD

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs due to a non-Gilead concomitant medication, must be reported as an AE.

7.4.2.3. Pregnancy Reporting Process

The investigator should report pregnancies in female study subjects and/or female partners of male subjects that are identified after initiation of study drug and throughout the study until 6 months after the last dose of study drugs to Gilead GLPS using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Contact details for transmitting the pregnancy report form are as follows:

Gilead GLPS: Gilead GLPS
Email: PPD
or
Fax: PPD

The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.

All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome after study must be reported to Gilead GLPS.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to Gilead GLPS using the pregnancy outcome report form. If the end of the pregnancy/partner pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead GLPS. Gilead GLPS contact information is as follows: email: PPD and fax: PPD

Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs which may be in the form of line-listings, serious adverse drug reactions, or suspected unexpected serious adverse reaction (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IRB/IEC in concerned member states of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the NCI CTCAE toxicity grading scale, Version 5.0. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.7. Toxicity Management

Severity should be recorded and graded according to NCI CTCAE v5.0 (Appendix 6**)**.

Toxicity should be managed according to Sections 5.5.1.3 and 5.5.1.4. Study drug will be discontinued for DLT during Part 1 or during safety run-in during Part 2 (Cohorts A and B) as defined in Section 3.2.1.1.1. Also refer to the ASCO Toxicity Management Guidelines (Appendix 3) and withhold or discontinue GS-3583 accordingly.

As per Section 5.5.1.1, GS-3583 dose modifications are not permitted in this study. GS-3583 administration may be delayed due to any AE that warrants a delay, as per Section 5.5.1.2. GS-3583 may be resumed as specified in Section 5.5.1.5.

8. STATISTICAL CONSIDERATIONS

Details of the statistical methods will be provided in the statistical analysis plan, including any deviations from the original statistical analyses planned.

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The objectives of this study are described in Section 2.

8.1.2. Endpoints: Part 1

8.1.2.1. Primary Endpoints

- Incidence of DLTs defined in Section 3.2.2.
- Incidence of AEs and laboratory abnormalities defined by NCI CTCAE v5.0.

8.1.2.2. Secondary Endpoints

- GS-3583 PK parameters (AUC_{tau})
- Rate of GS-3583 ADA

8.1.2.3. Other Endpoints of Interest

The exploratory endpoints of interest for Part 1 are as follows:

CCI

8.1.3. Endpoints: Part 2

8.1.3.1. Primary Endpoints

The primary endpoints for Part 2 Cohorts A and B are as follows:

- Incidence of DLTs defined in Section 3.2.2.
- Incidence of AEs and laboratory abnormalities defined by NCI CTCAE v5.0

8.1.3.2. Secondary Endpoints

The secondary endpoints for Part 2 Cohorts A and B are as follows:

- Confirmed ORR is defined as the percentage of subjects who have achieved confirmed CR or confirmed PR according to RECIST V1.1 and assessed by the investigator.
- Progression-free survival is the time from date of randomization until disease progression or death from any cause, whichever comes first as measured per RECIST V1.1 as assessed by the investigator
- Duration of response is measured from the time of first response (CR or PR) identified by RECIST V1.1 as assessed by the investigator until the date of first documented disease progression or death, whichever comes first.
- Overall survival is the length of time from date of randomization until the date of death from any cause.
- Disease control rate is measured by the percentage of subjects with a best overall confirmed response of CR or PR or stable disease.
- PK parameters (C_{max}, T_{max}, and AUC_{tau}) for GS-3583
- Rate of GS-3583 ADA

8.1.3.3. Other Endpoints of Interest

CCI

8.2. Planned Analyses

8.2.1. Interim Analysis

8.2.1.1. Part 1 Dose-Escalation Analysis and Part 2 Safety Run-in Analysis

For the purpose of making the decision whether to escalate to the next dose level/cohort, interim analyses of relevant safety and available PK data will be conducted by Gilead after all subjects in each cohort have completed dosing and the follow-up period in the DLT period as defined in Section 3.2.2. Safety assessments (eg, AEs, ECG, and laboratory results) will be displayed by cohort or dose level to facilitate the decision.

8.2.2. Final Analysis

The final analysis will be performed after all subjects have completed or discontinued from the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all subjects who received a study subject identification number. This will be the primary analysis set for by-subject listings.

8.3.1.2. DLT Analysis Set

The DLT Analysis Set includes all subjects who were enrolled for dose escalation, received all treatments of GS-3583 or combination therapy and completed safety procedures through DLT assessment period (inclusive of the last day) or experienced a DLT prior to end of DLT assessment period. Determination of MTD or RP2D will be based on the DLT Evaluable Analysis Set.

8.3.1.3. Safety Analysis Set

The Safety Analysis Set will include all subjects who received at least 1 dose of GS-3583 or combination therapy. This will be the primary analysis set for safety analysis.

8.3.1.4. Full Analysis Set

The Full Analysis Set includes all enrolled subjects who received at least 1 dose of GS-3583 or combination therapy (Part 1 and Part 2 Safety Run-in Cohorts) or all randomized subjects (Part 2 Randomized Expansion Cohorts). This will be the primary analysis set for efficacy analyses.

8.3.1.5. Pharmacokinetics Analysis Set

The PK Analysis Set includes all enrolled subjects who received at least 1 dose of GS-3583 or zimberelimab and have at least 1 nonmissing postdose concentration value reported by the PK laboratory. This will be the primary analysis set for all PK analyses.

8.3.1.6. Immunogenicity Analysis Set

The Immunogenicity Analysis Set includes all enrolled subjects who received at least 1 dose of GS-3583 or zimberelimab and had at least 1 ADA test. This will be the primary analysis set for immunogenicity data analyses.

8.3.1.7. Biomarker Analysis Set

The Biomarker Analysis Set includes all enrolled subjects who received at least 1 dose of GS-3583 or combination therapy and have at least 1 evaluable biomarker measurement available. This will be the primary analysis set for all biomarker data analyses.

8.3.2. Data Handling Conventions

In general, values for missing data will not be imputed. However, a missing pretreatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned; if the result of a continuous laboratory test is < 20.0, a value of 19.9 will be assigned).

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods.

Demographic summaries will include sex, race/ethnicity, and age.

Baseline data will include a summary of body weight, height, and body mass index.

8.5. Efficacy Analysis

For Part 1, efficacy analysis will be performed by dose level. For Part 2, efficacy analysis will be performed by cohort, dose level (for Safety Run-in Cohorts), or treatment (for Randomized Expansion Cohorts).

The ORR, DCR, and the respective corresponding 90% CI based on the Clopper-Pearson exact method {Clopper 1934} will be provided. Subjects who do not have sufficient baseline or on-study tumor assessment to characterize response will be counted as nonresponders.

PFS, DOR, and OS will be analyzed using Kaplan-Meier (KM) method. The median, 25% and 75% percentiles will be provided along with the corresponding 90% CI. In addition, the estimated rate at selected time point, such as 3 months, 6 months, 12 months, 18 months, and 24 months will be reported. The detailed censoring rules will be described in the statistical analysis plan.

The TTR will be summarized using descriptive statistics.

8.6. Safety Analysis

For Part 1, safety analysis will be performed by dose level. For Part 2, safety analysis will be performed by cohort, dose level (for Safety Run-in Cohorts), or treatment (for Randomized Expansion Cohorts).

All safety data collected on or after the date that study drug was first administered up to the last dose date plus 90 days will be analyzed according to the study drug received using the Safety Analysis Set.

For categorical safety data including incidence of AEs and categorizations of laboratory data, count and percentage of subjects will be summarized. For continuous safety data including laboratory data, descriptive summary statistics (mean, standard deviation, minimum, quartiles, median and maximum) will be summarized.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug data will be generated from the study drug administration data.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the MedDRA. System organ class, high-level group term, high-level term, preferred term, and lower-level term will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus 90 days.

Summaries (number and percentage of subjects) of treatment-emergent AEs (by system organ class and preferred term) will be provided.

8.6.3. Laboratory Evaluations

Selected laboratory data (using conventional units) will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the NCI CTCAE v5.0.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline up to and including the date of last dose of study drug plus 90 days, will be summarized. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent.

Laboratory abnormalities that occur before the first dose of study drug or after the subject has been discontinued from treatment for at least 90 days will be included in a data listing.

8.6.4. Other Safety Evaluations

Other safety measures such as vital signs, ECG, etc, will be summarized by treatment group.

8.7. Pharmacokinetic Analysis

For Part 1, PK analysis will be performed by dose level. For Part 2, PK analysis will be performed by cohort, dose level (for Safety Run-in Cohorts), or treatment (for Randomized Expansion Cohorts).

Serum concentrations for GS-3583 or zimberelimab will be summarized by nominal sampling time using descriptive statistics (ie, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum). Serum concentrations of GS-3583 or zimberelimab over time may be plotted in semilogarithmic and linear formats as mean ± standard deviation.

Pharmacokinetic parameters (AUC_{tau}, C_{max}, C_{trough}, T_{max}, CL, etc, as appropriate) will be listed and summarized using descriptive statistics.

8.8. Biomarker Analysis

For Part 1, biomarker analysis will be performed by dose level. For Part 2, biomarker analysis will be performed by cohort, dose level (for Safety Run-in Cohorts) or treatment (for Randomized Expansion Cohorts).

Pharmacodynamics data will be listed and summarized using descriptive statistics. Descriptive summaries for change from baseline will also be provided over time. Correlation of pharmacodynamic responses, immunologic changes with GS-3583 or combination therapy treatment, and other biomarkers with clinical response and/or safety may be explored as appropriate.

8.9. Immunogenicity Analysis

For Part 1, immunogenicity analysis will be performed by dose level. For Part 2, immunogenicity analysis will be performed by cohort, dose level (for Safety Run-in Cohorts) or treatment (for Randomized Expansion Cohorts).

Immunogenicity to GS-3583 or zimberelimab will be evaluated based upon the incidence of ADA formation. Number and percentage of positive or negative ADA results at each specified time point will be summarized using the Immunogenicity Analysis Set. Supporting data including treatment, nominal sampling day, actual date and time of sampling, and ADA results will be included in a listing.

8.10. Sample Size

A total of approximately 150 subjects will be enrolled.

For Part 1, assuming up to 4 planned dose levels will be tested with 3 DLT-evaluable subjects for the first dose level and up to 6 DLT-evaluable subjects per subsequent dose level, 21 DLT-evaluable subjects will be needed. Assuming 10% are not evaluable, approximately 24 subjects will be enrolled in Part 1.

For Part 2, a maximum of 63 subjects will be enrolled for each cohort. Six to 18 subjects will be evaluated in Safety Run-in Cohorts, and 45 subjects will be enrolled in Randomization Expansion Cohorts with 2:1 randomization ratio. The total maximum sample size in Part 2 is approximately 126.

The assessment of efficacy will be based on point estimate of ORR or the difference in ORR treatment effect with the confidence intervals. The exact 90% CI for various ORR or the differences are provided in Table 8-1 and Table 8-2.

Table 8-1. Exact 90% CI of ORR for a Sample Size of 30 in GS-3583 Combination Arm

Observed ORR	Exact 90% CI
20%	(9%, 36%)
30%	(17%, 47%)
40%	(25%, 57%)
50%	(34%, 66%)

ORR = objective response rate

Table 8-2. Exact 90% CI of Difference in ORR for a Sample Size of 45 with 2:1 Randomization Ratio

Observed ORR (GS-3583 vs Control) (Difference)	Exact 90% CI
30% vs 20% (10%)	(−15%, 31%)
50% vs 40% (10%)	(−18%, 36%)
40% vs 20% (20%)	(−5%, 41%)
53.3% vs 33.3% (20%)	(−8%, 44%)

ORR = objective response rate

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Gilead or proprietary interests in the study drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved informed consent form for documenting written informed consent. Each ICF (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative, the person conducting the consent discussion, and an impartial witness (if required by IRB or IEC or local requirements).

The ICF will inform subjects about genomic testing and/or planned sample retention. CCI

[redacted]

9.1.5. Confidentiality

The investigator must ensure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead or the laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log with details for all subjects screened and enrolled in the study, in accordance with the site procedures and regulations. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, eCRFs, study drug information, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRFs, and governmental approval with correspondence, the ICFs, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification
- Documentation that subject meets eligibility criteria, ie, medical history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date, causality and severity), and documentation that adequate medical care has been provided for any AE
- Concomitant medication (including start and end date, dose, if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.7. Case Report

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the EDC system. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures. The inclusion/exclusion criteria and enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the eCRF completion guidelines provided by the sponsor. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. At a minimum, prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her login credentials to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agencies when applicable and in accordance with local regulatory requirements. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases. For studies with sites in countries following the EU Regulation No. 536/2014, a CSR will be submitted within 1 year after the global end of study (as defined in Section 3.6).

Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Gilead clinical trial agreement.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries in the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on-site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the subjects, appropriate regulatory authority, IRBs, and ethics committee. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404

STUDY ACKNOWLEDGMENT

A Phase 1b Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of GS-3583, a FLT3 Agonist Fc Fusion Protein, as Monotherapy and in Combination with Anticancer Therapies in Subjects with Advanced Solid Tumors

GS-US-496-5657, Protocol Amendment 2, 14 April 2022

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

Name (Printed)
Medical Monitor

[See appended electronic signature]

Signature

[See appended electronic signature]

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with subjects being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Study drug supplies to subjects and sites:

    a) Subjects may be unable to return to the site for a number of visits to get the study drug, or the site may be unable to accept any subject visits. Without study drug, the subject would not be able to stay on the study drug as planned per protocol.

        Mitigation plan: Since this study is an oncology study the care subjects receive is considered essential therefore there should not be an interruption of visits where subjects receive study drug due to the pandemic, in most cases.

    b) Shipments of study drug could be delayed because of transportation issues. Without study drug, subject would not be able to stay on the study drug as planned per protocol.

        Mitigation plan: The sites' study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and study sites. Manual shipments will be triggered as necessary.

2) Subject safety monitoring and follow-up:

    a) Subjects may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol.

        Mitigation plan: For subjects who may be unable or unwilling to visit the study site for their scheduled study visits as required per protocol, the principal investigator or qualified delegate will conduct a virtual study visit, via phone or video conferencing, to assess the subject within target visit window date, whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

        i) Confirm if subject has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AE/SAEs.

        ii) Review current list of concomitant medications and document any new concomitant medications.

    b) Subjects may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be sent for central lab analyses.

Mitigation plan: Local labs may be utilized as appropriate to monitor subject safety until the subject can return to the site for their regular follow-up per protocol. Any laboratory assessments conducted at a local lab due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local lab pregnancy testing is not feasible.

c) Subjects may be unable or unwilling to attend the study visit to sign an updated informed consent form (ICF) version.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local ethics committee (EC)/ institutional review board (IRB) and national laws and regulations. Remote consent will be allowed if it has been approved by the local EC/IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

3) Protocol and monitoring compliance:

a) Protocol deviations may occur, in case scheduled visits cannot occur as planned per protocol.

Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed subject visits or deviation to the protocol due to the pandemic must be reported in the electronic case report form (eCRF) and described in the clinical study report. Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

b) Monitors may be unable to carry out source data review or source data verification (SDV), or study drug accountability or assess protocol and Good Clinical Practice (GCP) compliance. This may lead to delays in SDV, an increase in protocol deviations, or under reporting of AEs.

Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. In compliance with Gilead policy, remote SDV should not be arranged. The study monitor is to reference the study monitoring plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or subjects on site, must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

a) There may be an increased amount of missing data due to subjects missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

5) Concurrent administration of the COVID-19 vaccine:

There may be potential safety issues due to concurrent administration of the COVID-19 vaccine and study drugs.

Mitigation plan: There is not substantial safety data regarding the concurrent administration of the COVID-19 vaccine and zimberelimab, 5-fluorouracil (5-FU), cisplatin, carboplatin, and docetaxel. Subjects are allowed to receive the COVID-19 vaccine to reduce the risk and complications of COVID-19 infection. Investigators and study personnel should provide close surveillance of subjects after COVID-19 vaccine administration and the institutional guidelines should always be followed. The administration of specific COVID-19 vaccine must be documented in the clinical database and AEs associated with COVID-19 vaccine administration should be recorded in the AE eCRF. The COVID-19 vaccine administration should be recorded in the prior or concomitant medication eCRF as appropriate. The study visits should continue as planned, if possible, and clinically appropriate if vaccination occurs while the subject is on the study.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of subjects who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of study drug(s) in study subjects remains unchanged.

Appendix 3. American Society of Clinical Oncology (ASCO) Toxicity Management Guidelines

https://ascopubs.org/doi/full/10.1200/JCO.21.01440

Appendix 4. Study Procedures Tables

Appendix Table 1. Part 1 Study Procedures – Screening

Assessment	
Administrative Procedures	**Day −28 to −1**
Informed consent	X
Review of inclusion/exclusion criteria	X
Review of medical history, including smoking status and demographics	X
Review of baseline symptoms	X
Review of prior and concomitant medications	X
Cancer disease details and prior treatment	X
Enrollment[a]	X
Clinical Procedures/Assessments	**Day −28 to −1**
Review AEs[b]	X
Full PE	X
Vital signs and weight[c]	X
Height	X
12-lead ECG	X
Echocardiogram or MUGA[d]	X
ECOG Performance Status	X
Imaging Assessments	**Day −28 to −1**
Tumor imaging[e]	X
Laboratory Procedures/Assessments	**Day −28 to −1**
Serum chemistry	X
Hematology tests	X
Coagulation tests	X
Endocrine function tests	X
HIV screening	X
HBV & HCV serology	X
Urinalysis	X
Serum pregnancy test	X
Biomarker Procedures/Assessments	**Day −28 to −1**
Whole blood for CHIP mutation analysis[f]	X
Whole blood for circulating tumor DNA[f]	X
Collection of pretreatment tumor biopsy (archival and fresh)	X

AEs = adverse events; CHIP = clonal hematopoiesis of indeterminate potential; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCV = hepatitis C virus; MUGA = multigated acquisition; PE = physical exam; SAE = serious adverse event

a Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study within 28 days after screening.
b After informed consent, but prior to initiation of study medication, all SAEs and AEs related to protocol-mandated procedures will be reported on Case Report Forms.
c Vital signs will only be measured while subject is in sitting, semi-recumbent or supine position.
d Complete echocardiogram assessment will be conducted at screening to establish a baseline. A MUGA scan is allowed.
e The initial tumor imaging will be performed within 28 days prior to first dose of study drug. Scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and ≤ 28 days prior to first dose of study drug.
f Biomarker Assays: See details on all biomarker sample collections in Section 6.5.2.1.

Appendix Table 2. Part 1 Study Procedures – Treatment Phase

	Treatment Phase																			
	Cycle 1							Cycle 2		Cycle 3							Cycle 4 & Every Even Cycle After		Cycle 5 & Every Odd Cycle After	
Study Visits (Cycle Day)	**1**	**2**	**3**	**5**	**8**	**15**	**24**	**1**	**15**	**1**	**2**	**3**	**5**	**8**	**15**	**24**	**1**	**15**	**1**	**15[a]**
Visit Window (Days)[b]	—	—	—	—	—	—	—	+2	+2	+2	—	—	—	—	—	—	+2	+2	+2	+2
Visit Schedule (Hours Postinfusion)	—	24	48	96	168	336	552	—	336	—	24	48	96	168	336	552	—	336	—	336
Administrative Procedures																				
Review of inclusion/exclusion criteria	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Review of baseline symptoms	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Review of prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments[c]																				
Review AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Focused PE	X[c]	—	—	—	—	X[c]	—	X[c]	—	X[c]	—	—	—	—	X	—	X[c]	—	X[c]	—
Vital signs and weight[d]	X[d]	—	—	—	—	X[d]	—	X[d]	—	X[d]	—	—	—	—	X	—	X[d]	—	X[d]	—
12-lead ECG	X[e]	—	—	—	—	X[f]	—	X[f]	—	X[f]	—	—	—	—	—	—	—	—	X[f]	—
ECOG Performance Status	X[c]	—	—	—	—	—	—	X[c]	—	X[c]	—	—	—	—	—	—	X[c]	—	X[c]	—
Imaging Assessments																				
Tumor imaging[g]	Every 8 weeks																			
Laboratory Procedures/Assessments[h]																				
Serum chemistry	X[c]	—	—	—	X	X[c]	—	X[c]	X	X[c]	—	—	—	—	X	—	X[c]	—	X[c]	—
Hematology tests	X[c]	—	—	—	X	X[c]	—	X[c]	X	X[c]	—	—	—	—	X	—	X[c]	—	X[c]	—
Coagulation tests	—	—	—	—	—	X[c]	—	X[c]	—	X[c]	—	—	—	—	—	—	X[c]	—	X[c]	—
Endocrine function tests	—	—	—	—	—	X[c]	—	X[c]	—	X[c]	—	—	—	—	—	—	X[c]	—	X[c]	—
Urinalysis	X[c]	—	—	—	X	X[c]	—	X[c]	X	X[c]	—	—	—	—	X	—	X[c]	—	X[c]	—
Urine pregnancy test[i]	X[c]	—	—	—	—	X[c]	—	X[c]	—	X[c]	—	—	—	—	—	—	X[c]	—	X[c]	—
Blood for PK assays[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		—
Blood for ADA assays[k]	X	—	—	—	—	—	—	X	—	X	—	—	—	—	—	—	X[l]	—	X[m]	—

	Treatment Phase																			
	Cycle 1							Cycle 2		Cycle 3							Cycle 4 & Every Even Cycle After		Cycle 5 & Every Odd Cycle After	
Study Visits (Cycle Day)	**1**	**2**	**3**	**5**	**8**	**15**	**24**	**1**	**15**	**1**	**2**	**3**	**5**	**8**	**15**	**24**	**1**	**15**	**1**	**15[a]**
Visit Window (Days)[b]	—	—	—	—	—	—	—	+2	+2	+2	—	—	—	—	—	—	+2	+2	+2	+2
Visit Schedule (Hours Postinfusion)	—	**24**	**48**	**96**	**168**	**336**	**552**	—	**336**	—	**24**	**48**	**96**	**168**	**336**	**552**	—	**336**	—	**336**
Biomarker Procedures/Assessments[h]																				
Whole blood for pharmacodynamic biomarkers (PBMC and plasma)[n]	X[o]	—	—	—	X	X[o]	X	X[o]	X	X[o]	—	—	—	X	X	X	X[o]	X	—	—
Whole blood for blood cell count[n]	X[o]	—	—	—	X	X[o]	X	X[o]	X	X[o]	—	—	—	X	X	X	X[o]	X	—	—
Whole blood for CHIP mutation analysis[n]	X	—	—	—	—	—	—	X	—	X	—	—	—	—	—	—	X	—	—	—
Whole blood for TCR sequencing[n]	X	—	—	—	—	—	—	X	—	X	—	—	—	—	—	—	X	—	—	—
Whole blood for circulating tumor DNA[n]	X	—	—	—	—	—	—	X	—	X	—	—	—	—	—	—	X	—	—	—
Whole blood for Paxgene RNA[n]	X	—	—	—	—	X	—	X	—	X	—	—	—	—	X	—	X	—	—	—
Serum pharmacodynamics for circulating factors[n]	X	—	—	—	X	X	X	X	—	X	—	—	—	X	X	—		—	—	—
Stool sample for microbiome sequencing[n]	X	—	—	—	—	—	—	—	—	X	—	—	—	—	—	—	—	—	—	—
CCI [redacted] CCI																				
Study Drug Administration																				
GS-3583[r]	X	—	—	—	—	X	—	X	—	X	—	—	—	—	—	—	X	—	X	—

ADA = antidrug antibody; AEs = adverse events; CHIP = clonal hematopoiesis of indeterminate potential; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; MUGA = multigated acquisition; PBMC = peripheral blood mononuclear cell; PE = physical exam; PK = pharmacokinetic(s); TCR = T-cell receptor

a The Day 15 visit of Cycle 5 and every odd cycle thereafter, including Cycle 13, will be conducted via telephone. However, this visit may be performed in-clinic per the investigator's discretion.
b Treatment administration and associated procedures for a visit may be delayed for treatment-related AEs beyond the window and subsequent schedule adjusted accordingly.
c On each day of study drug administration, the predose focused PE, ECOG performance status, and safety labs (hematology, chemistry, coagulation [applicable visits], endocrine function tests [applicable visits], urinalysis, and urine pregnancy) can be performed within 72 hours prior to each dose of study treatment.
d Vital signs will only be measured while subject is in sitting, semi-recumbent or supine position. Vital signs are to be measured prior to each infusion commencing and at the end of each infusion. For the first 2 doses during Cycle 1, vital signs will be measured 1 hour (±15 minutes) after the end of the GS-3583 infusion. Thereafter in subsequent cycles, the posttreatment vital signs can be taken 30 minutes (-10/+20 minutes) after the end of each GS-3583 infusion. Subjects will remain in the clinic under close supervision for the duration of this monitoring period.
e On Cycle 1 Day 1, 12-lead ECG will be collected before and 2 hours (-10/+20 minutes) after the end of GS-3583 administration.

f On Cycle 1 Day 15, Cycle 2 Day 1, and at every odd numbered cycle starting at Cycle 3, posttreatment 12-lead ECGs will be collected on Day 1 at 30 minutes (-10/+20 minutes) after the end of each GS-3583 infusion. An ECG will also be collected at the EOT visit and 60-day follow-up.

g The initial tumor imaging will be performed within 28 days prior to first dose of study drug. Scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and ≤ 28 days prior to first dose of study drug. On-study imaging will be performed every 8 weeks from first treatment dose and will continue until progressive disease as assessed by the investigator, a new line of anticancer therapy is initiated, or up to 1 year after the last dose of study drug, whichever occurs first. For subjects who permanently discontinue from the study in the absence of progressive disease/or start of a new line of anticancer therapy and will not be continuing tumor imaging during the posttreatment period, additional imaging is recommended at the EOT visit if the last imaging was performed more than 30 days prior. For subjects that met progressive disease clinically, subjects will continue tumor imaging until progressive disease is confirmed radiographically or prior to the start of a new line of anticancer therapy. The timing of on-study treatment imaging should follow calendar days and should not be adjusted for delays in treatment administration or for visits.

h Unless otherwise specified, samples should be collected before treatment administration. Refer to the laboratory manual for instructions and additional information.

i Urine pregnancy tests will be performed locally at each site. A negative result must be confirmed at every visit prior to study drug infusion.

j PK Assays: See details of all PK sample collections in Section 6.5.1.2 and Table 6-3.

k ADA Assays: Assessed at predose (≤ 30 minutes before start of infusion) at Day 1 of Cycles 1, 2, 3, 4, 7, and 13; and at the 60-day follow-up visit (approximately 60 days after the last dose of study drug). An additional blood sample will be collected at the EOT visit if a subject terminates early from study treatment.

l ADA samples will be collected at Cycle 4 only.

m ADA samples will be collected at Cycles 7 and 13 only.

n Biomarker Assays: See details on all biomarker sample collections in Section 6.5.2.1. Please note that two 10 mL samples will be collected at all time points except on Days 8 and 24 in Cycles 1 and 3, when only 1 sample of 10 mL will be collected.

o The predose whole blood samples for Pharmacodynamic Biomarkers and Blood Cell Count will be collected any time prior to the start of infusion at the Day 1 visit. However, for Cycle 1 Day 1, an additional set of predose samples should also be collected up to 72 hours prior to the Cycle 1 Day 1 visit, if feasible.

p CCI [redacted]

q CCI [redacted]

r GS-3583 will be administered intravenously within 60 minutes (± 10 minutes) every 4 weeks on Day 1 of each cycle, with an additional dose administered on Cycle 1 Day 15. Subjects must be observed for 1-hour postinfusion for infusion-related reaction for the first 2 doses during Cycle 1 and thereafter, 30 minutes after the end of the GS-3583 infusion. Refer to section 5.5.1.3 for more information. If administration of GS-3583 is delayed due to an AE, treatment visits may be delayed and schedules for subsequent visits should be adjusted accordingly.

Appendix Table 3. Part 1 Study Procedures Table – Posttreatment

	End of Treatment	Posttreatment		Survival Follow-Up
	Within 7 Days After Last Dose of Study Treatment or EOT Decision	60-day Follow-up Visit[a,b,c]	≤ 1 Year From Last Dose[b]	≤ 1 Year From Last Tumor Lesion Assessment[b,c,d]
Visit Window	**≤ 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**
Administrative Procedures				
Review of prior and concomitant medication	X	X	—	—
Subsequent anticancer therapy status	X	X	X	X
Overall survival[b,c,d]	—	—	—	X
Clinical Procedures/Assessments				
Review AEs	X	X	—	—
Full PE	X	—	—	—
Focused PE	—	X	—	—
Vital signs and weight[e]	X	X	—	—
12-Lead ECG	X	X	—	—
ECOG Performance Status	X	X	—	—
Imaging Assessments				
Tumor imaging[f]	Every 8 weeks			—
Laboratory Procedures/Assessments				
Serum chemistry	X	X	—	—
Hematology tests	X	X	—	—
Coagulation tests	X	X	—	—
Endocrine function tests	X	X	—	—

	End of Treatment	Posttreatment		Survival Follow-Up
	Within 7 Days After Last Dose of Study Treatment or EOT Decision	60-day Follow-up Visit[a,b,c]	≤ 1 Year From Last Dose[b]	≤ 1 Year From Last Tumor Lesion Assessment[b,c,d]
Visit Window	**≤ 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**
Urinalysis	X	X	—	—
Urine pregnancy test[g]	X	X	X[g]	—
Blood for PK assays[h]	X[i]	X	—	—
Blood for ADA assays[j]	X[i]	X	—	—
Biomarker Procedures/Assessments				
Whole blood for pharmacodynamic biomarkers (PBMC and plasma)[k]	X[i]	X	—	—
Whole blood for blood cell count[k]	X[i]	X	—	—
Whole blood for CHIP mutation analysis[k]	X	—	—	—
Whole blood for TCR sequencing[k]	X	—	—	—
Whole blood for circulating tumor DNA[k]	X	—	—	—
Whole blood for Paxgene RNA[k]	X	—	—	—
Serum pharmacodynamics for circulating factors[k]	X	—	—	—
Stool sample for microbiome sequencing[k]	X	—	—	—
CCI				

ADA = antidrug antibody; AEs = adverse events; CHIP = clonal hematopoiesis of indeterminate potential; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; MUGA = multigated acquisition; PBMC = peripheral blood mononuclear cell; PE = physical exam; PK = pharmacokinetic(s); SAE = serious adverse event; TCR = T-cell receptor

a All subjects who discontinue treatment will have a follow-up visit 60 days (± 7 days) after the last dose of study drug.
b Subjects who discontinue treatment due to reasons other than progressive disease and/or start of a new line of anticancer therapy will complete the 60-day follow-up and continue tumor imaging assessments at the predefined schedule until documented progressive disease, initiation of a new anticancer therapy, or up to 1 year after the last dose of study drug, whichever occurs first; and then move into survival follow-up for up to 1 year after the completion/discontinuation of tumor lesion assessments.
c Subjects who discontinue due to progressive disease and/or start of a new line of anticancer therapy will complete the 60-day follow-up and then enter the survival follow-up period for up to 1 year after the completion/discontinuation of tumor lesion assessments.
d During the survival follow-up period, subjects will be contacted by telephone to assess for survival status and any new malignancies every 3 months for up to 1 year after the completion/discontinuation of tumor lesion assessments. No imaging assessment is required for survival follow-up. Any new malignancies will be reported as SAEs.

e Vital signs will only be measured while subject is in sitting, semi-recumbent, or supine position.
f On-study imaging will be performed every 8 weeks from first dose of study drug and will continue until progressive disease as assessed by the investigator, a new line of anticancer therapy is initiated, or up to 1 year after the last dose of study drug, whichever occurs first. For subjects who permanently discontinue from the study in the absence of progressive disease/or start of a new line of anticancer therapy and will not be continuing tumor imaging during the posttreatment period, additional imaging is recommended at the EOT visit if the last imaging was performed more than 30 days prior. For subjects that met progressive disease clinically, subjects will continue tumor imaging until progressive disease is confirmed radiographically or prior to the start of a new line of anticancer therapy. The timing of on-study treatment imaging should follow calendar days and should not be adjusted for delays in treatment administration or for visits.
g Urine pregnancy tests will be performed locally at each site. After the 60-day follow-up visit, urine pregnancy tests will be performed monthly until 12 weeks after the last dose of study drug (Appendix 5).
h PK Assays: See details of all PK sample collections in Table 6-3.
i Blood samples will only be collected at the EOT visit for subjects that terminate early from study treatment.
j ADA Assays: Assessed at the 60-day follow-up visit (approximately 60 days after the last dose of study drug). An additional blood sample will be collected at the EOT visit if a subject terminates early from study treatment.
k Biomarker Assays: See details on all biomarker sample collections in Section 6.5.2.1.
l CCI [redacted]

Appendix Table 4. Part 2 Study Procedures – Screening

Assessment	
Administrative Procedures	**Day −28 to −1**
Informed consent	X
Review of inclusion/exclusion criteria	X
Review of medical history, including smoking status and demographics	X
Review of baseline symptoms	X
Review of prior and concomitant medications	X
Cancer disease details and prior treatment	X
Enrollment/Randomization[a]	X
Clinical Procedures/Assessments	**Day −28 to −1**
Review AEs[b]	X
Full PE	X
Vital signs and weight[c]	X
Height	X
12-lead ECG	X
Echocardiogram or MUGA[d]	X
ECOG Performance Status	X
Imaging Assessments	**Day −28 to −1**
Tumor imaging[e]	X
Laboratory Procedures/Assessments	**Day −28 to −1**
Serum chemistry	X
Hematology tests	X
Coagulation tests	X
Endocrine function tests	X
HIV screening	X
HBV & HCV serology	X
HPV P16 expression testing as indicated (Part 2 Cohort A [HNSCC] subjects only)	X
Baseline combined positive score (CPS) (Part 2 Cohort A [HNSCC] subjects only)	X
Urinalysis	X
Serum pregnancy test	X
Biomarker Procedures/Assessments	**Day −28 to −1**
Whole blood for CHIP mutation analysis[f]	X
Whole blood for circulating tumor DNA[f]	X

Assessment	
Collection of pretreatment tumor biopsy[g]	X
Collection of mandatory fresh baseline tumor biopsy (Randomized Expansion Cohorts only)[h]	X
Cohort B (NSCLC) only: Baseline information on PD-L1 expression at initial diagnosis, EGFR, ALK, ROS1, or any other known actionable genomic alterations	X

AEs = adverse events; ALK = anaplastic lymphoma kinase; CHIP = clonal hematopoiesis of indeterminate potential; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; HBV = hepatitis B virus; HCV = hepatitis C virus; HNSCC = head and neck squamous cell carcinoma; HPV = human papillomavirus; MUGA = multigated acquisition; PD-L1 = programmed cell death ligand 1; PE = physical exam; SAE = serious adverse event

a Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be enrolled/randomized into the study within 28 days after screening.

b After informed consent, but prior to initiation of study medication, all SAEs and AEs related to protocol-mandated procedures will be reported on Case Report Forms.

c Vital signs will only be measured while subject is in sitting, semi-recumbent, or supine position.

d Complete echocardiogram assessment will be conducted at screening to establish a baseline. A MUGA scan is allowed.

e The initial tumor imaging will be performed within 28 days prior to first dose of study drug. Scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and ≤ 28 days prior to first dose of study drug.

f Biomarker Assays: See details on all biomarker sample collections in Section 6.5.2.1.

g Collection of archival tumor biopsy as formalin-fixed paraffin-embedded (FFPE) blocks or 10 to 25 unstained slides. If archival tumor tissue is not available or insufficient, collection of fresh tumor biopsy from subjects is strongly preferred. Please refer to Section 6.5.2.1

h Each subject enrolled in the Randomized Expansion Cohorts shall undergo a mandatory tumor biopsy if the investigator considers that no undue risk is posed to the subjects due to biopsy related procedures. A fresh archival tumor biopsy obtained after the end of the last line of therapy and not older than 6 months may be substituted for the baseline biopsy.

Appendix Table 5. Part 2 Study Procedures – Treatment Phase

	Treatment Phase															
	Cycle 1					Cycle 2		Cycle 3					Cycle 4 & Every Even Cycle After		Cycle 5 & Every Odd Cycle After	
Study Visits (Cycle Day)	**1**	**8**	**12**	**15**	**21**	**1**	**15**	**1**	**8**	**12**	**15**	**21**	**1**	**15**	**1**	**15[a]**
Visit Window (Days)[b]	—	—	—	—	—	+2	+2	+2	—	—	—	—	+2	+2	+2	+2
Visit Schedule (Hours Postinfusion)	—	168	264	336	—	—	336	—	168	264	336	—	—	336	—	336
Administrative Procedures																
Review of inclusion/exclusion criteria	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Review of disease history	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Review of baseline symptoms	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Review of prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments[c]																
Review AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Focused PE	X[c]	—	—	—	—	X[c]	—	X[c]	—	—	—	—	X[c]	—	X[c]	—
Vital signs and weight[d]	X[d]	—	—	—	—	X[d]	—	X[d]	—	—	—	—	X[d]	—	X[d]	—
12-lead ECG	X[e]	—	—	—	—	X[f]	—	X[f]	—	—	—	—	—	—	X[f]	—
ECOG Performance Status	X[c]	—	—	—	—	X[c]	—	X[c]	—	—	—	—	X[c]	—	X[c]	—
Imaging Assessments																
Tumor Imaging[g]	Every 6 weeks (± 7 days) from the first dose of study drug until Week 24, then every 9 weeks thereafter (Week 33, Week 42, etc.)															
Laboratory Procedures/Assessments[h]																
Serum chemistry	X[c]	X	—	—	—	X[c]	—	X[c]	—	—	—	—	X[c]	—	X[c]	—
Hematology tests	X[c]	—	—	—	—	X[c]	—	X[c]	—	—	—	—	X[c]	—	X[c]	—
Coagulation tests	—	—	—	—	—	X[c]	—	X[c]	—	—	—	—	X[c]	—	X[c]	—
Endocrine function tests	—	—	—	—	—	X[c]	—	X[c]	—	—	—	—	X[c]	—	X[c]	—
Urinalysis	X[c]	X	—	—	—	X[c]	—	X[c]	—	—	—	—	X[c]	—	X[c]	—
Urine pregnancy test[i]	X[c]	—	—	—	—	X[c]	—	X[c]	—	—	—	—	X[c]	—	X[c]	—
Blood for PK assays[j] (GS-3583) – Safety Run-in Cohorts A and B	X	X	—	X	—	X	—	X	X	—	X	—	—	—	X	—
Blood for PK assays[j] (GS-3583) – Randomized Expansion Cohorts A and B	X	—	—	—	—	X	—	X	—	—	—	—	—	—	X	—

	Treatment Phase															
	Cycle 1					Cycle 2		Cycle 3					Cycle 4 & Every Even Cycle After		Cycle 5 & Every Odd Cycle After	
Study Visits (Cycle Day)	**1**	**8**	**12**	**15**	**21**	**1**	**15**	**1**	**8**	**12**	**15**	**21**	**1**	**15**	**1**	**15[a]**
Visit Window (Days)[b]	—	—	—	—	—	+2	+2	+2	—	—	—	—	+2	+2	+2	+2
Visit Schedule (Hours Postinfusion)	—	**168**	**264**	**336**	—	—	**336**	—	**168**	**264**	**336**	—	—	**336**	—	**336**
Blood for PK assays[j] (zimberelimab) – Safety Run-in and Randomized Expansion Cohort A	X	—	—	—	—	X	—	X	—	—	—	—	—	—	X	—
Blood for ADA assays[k]	X	—	—	—	—	X	—	X	—	—	—	—	—	—	X	—
Biomarker Procedures/Assessments[h]																
Whole blood for pharmacodynamic biomarkers (PBMC and plasma)[l] – Safety Run-in Cohorts A and B	X[m]	—	X	X	—	X[m]	X[m]	X[m]	—	X	X	—	X[m]	X[m]	—	—
Whole blood for pharmacodynamic biomarkers (PBMC and plasma)[l] – Randomized Expansion Cohorts A and B	X[m]	—	—	X[m]	—	X[m]	X[m]	X[m]	—	—	X[m]	—	X[m]	X[m]	—	—
Whole blood for blood cell count[l] – Safety Run-in Cohorts A and B	X[m]	—	X	X	—	X[m]	X[m]	X[m]	—	X	X	—	X[m]	X[m]	—	—
Whole blood for blood cell count[l] – Randomized Expansion Cohorts A and B	X[m]	—	—	X[m]	—	X[m]	X[m]	X[m]	—	—	X[m]	—	X[m]	X[m]	—	—
Whole blood for TCR sequencing	X	—	—	—	—	X	—	X	—	—	—	—	X	—	—	—
Whole blood for CHIP mutation analysis	X	—	—	—	—	X	—	X	—	—	—	—	X	—	—	—
Whole blood for circulating tumor DNA	X	—	—	—	—	X	—	X	—	—	—	—	X	—	—	—
Whole blood for Paxgene RNA	X[m]	—	—	X	—	X[m]	—	X[m]	—	—	X	—	X[m]	—	—	—
Serum pharmacodynamics for circulating factors	X[m]	—	—	X	—	X[m]	—	X[m]	—	—	X	—	—	—	—	—
Stool sample for microbiome sequencing	X[m]	—	—	—	—	—	—	X[m]	—	—	—	—	—	—	—	—
CCI																
Collection of mandatory on-treatment tumor biopsy (Randomized Expansion Cohorts only)[o]	—	—	—	—	—	—	X	—	—	—	—	—	—	—	—	—
Study drug administration																
GS-3583[p]	X	—	—	—	—	X	—	X	—	—	—	—	X	—	X	—
Cohort A: Zimberelimab[q]	X	—	—	—	—	X	—	X	—	—	—	—	X	—	X	—
Cohort A: Cisplatin[q] or Carboplatin[q]	X	—	—	—	—	X	—	X	—	—	—	—	X (C4, C6)	—	X (C5)	—
Cohort A: 5-FU[q]	X[r]	—	—	—	—	X[r]	—	X[r]	—	—	—	—	X[r] (C4, C6)	—	X[r] (C5)	—
Cohort B: Docetaxel[q]	X	—	—	—	—	X	—	X	—	—	—	—	X	—	X	—

ADA = antidrug antibody; AEs = adverse events; C = Cycle; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; 5-FU = 5-fluorouracil; MUGA = multigated acquisition; PBMC = peripheral blood mononuclear cell; PE = physical exam; PK = pharmacokinetic(s); TCR = T-cell receptor

a The Day 15 visit of Cycle 5 and every odd cycle thereafter will be conducted via telephone. However, this visit may be performed in-clinic per the investigator's discretion.
b Treatment administration and associated procedures for a visit may be delayed for treatment-related AEs beyond the window and subsequent schedule adjusted accordingly.
c On each day of study drug administration, the predose focused PE, ECOG performance status, and safety labs (hematology, chemistry, coagulation [applicable visits], endocrine function tests [applicable visits], urinalysis, and urine pregnancy) can be performed within 72 hours prior to each dose of study treatment.
d Vital signs will only be measured while subject is in sitting, semi-recumbent or supine position. Vital signs are to be measured prior to each infusion commencing and at the end of each infusion. For the first dose during Cycle 1, vital signs will also be measured 1 hour (±15 minutes) after the end of the GS-3583 infusion. Thereafter in subsequent cycles, the posttreatment vital signs can be taken 30 minutes (-10/+20 minutes) after the end of each GS-3583 infusion. Subjects will remain in the clinic under close supervision for the duration of this monitoring period.
e On Cycle 1 Day 1, 12-lead ECG will be collected before and 2 hours (-10/+20 minutes) after the end of GS-3583 administration.
f On Cycle 2 Day 1 and at every odd numbered cycle starting at Cycle 3, posttreatment 12-lead ECGs will be collected on Day 1 at 30 minutes (-10/+20 minutes) after the end of each GS-3583 infusion.
g The initial tumor imaging will be performed within 28 days prior to first dose of study drug. Scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and ≤ 28 days prior to first dose of study drug. On-study imaging will continue until progressive disease as assessed by the investigator, a new line of anticancer therapy is initiated, or up to 1 year after the last dose of study drug, whichever occurs first. For subjects who permanently discontinue from the study in the absence of progressive disease/or start of a new line of anticancer therapy and will not be continuing tumor imaging during the posttreatment period, additional imaging is recommended at the EOT visit if the last imaging was performed more than 30 days prior. For subjects that met progressive disease clinically, subjects will continue tumor imaging until progressive disease is confirmed radiographically or prior to the start of a new line of anticancer therapy. The timing of on-study treatment imaging should follow calendar days and should not be adjusted for delays in treatment administration or for visits.
h Unless otherwise specified, samples should be collected before treatment administration. Refer to the laboratory manual for instructions and additional information.
i Urine pregnancy tests will be performed locally at each site. A negative result must be confirmed at every visit prior to study drug infusion.
j PK Assays: See details of all PK sample collections in Section 6.5.1.2, Table 6-4, and Table 6-5.
k ADA Assays for GS-3583 (Cohorts A and B) and Zimberelimab (Cohort A): Assessed at predose (≤ 30 minutes before start of infusion) at Day 1 of Cycle 1, 2, 3, 5, 9, 17.
l The predose whole blood samples for Pharmacodynamic Biomarkers and Blood Cell Count will be collected any time prior to the start of infusion at the Day 1 visit. However, for Cycle 1 Day 1, an additional set of predose samples should also be collected up to 72 hours prior to the Cycle 1 Day 1 visit, if feasible.
m Sample collected predose.
n CCI [redacted]
o On-treatment fresh tumor biopsy will only be collected if a fresh pretreatment tumor biopsy or a recent archival tumor biopsy was collected. The on-treatment fresh tumor biopsy will be collected any time after Day 15 of Cycle 2, but strongly preferred between Day 15 of Cycles 2 and 4 after completion of radiographic imaging, from subjects in the Randomized Expansion Cohorts only.
p GS-3583 will be administered intravenously within 60 minutes (± 10 minutes) every 21 days on Day 1 of each cycle for a maximum of 8 cycles. Subjects must be observed for 1-hour postinfusion for infusion-related reaction for the first 2 doses and thereafter, 30 minutes after the end of the GS-3583 infusion. Refer to Section 5.4.1 for more information. If administration of GS-3583 is delayed due to an AE, treatment visits may be delayed and schedules for subsequent visits should be adjusted accordingly.
q Premedication is required prior to drug administration. Refer to Section 5.4.2 for premedication requirements.
r On Day 1 of each treatment cycle, 5-FU will be administered as a continuous intravenous infusion over 4 days. For more information, refer to Table 5-3.

Appendix Table 6. Part 2 Study Procedures Table – Posttreatment

	End of Treatment	Posttreatment		Survival Follow-up
	Within 7 Days After Last Dose of Study Treatment or EOT Decision	60-Day Follow-up Visit[a,b,c]	≤ 1 year from last dose[b]	≤ 1 year from last tumor lesion assessment[b,c,d]
Visit Window	**≤ 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**
Administrative Procedures				
Review of prior and concomitant medication	X	X	—	—
Subsequent anticancer therapy status	X	X	X	X
Clinical Procedures/Assessments				
Review AEs	X	X	—	—
Full physical examination	X	—	—	—
Focused physical exam	—	X	—	—
Vital signs and weight[e]	X	X	—	—
12-Lead ECG	X	X	—	—
ECOG Performance Status	X	X	—	—
Imaging Assessments				
Tumor Imaging[f]	Every 6 weeks (± 7 days) from the first treatment dose until Week 24, then every 9 weeks thereafter starting at Week 33			—
Laboratory Procedures/Assessments				
Serum chemistry	X	X	—	—
Hematology tests	X	X	—	—
Coagulation tests	X	X	—	—
Endocrine function tests	X	X	—	—
Urinalysis	X	X	—	—
Urine pregnancy test[g]	X	X	X[g]	—
Blood for PK assays[h] (GS-3583) – Safety Run-in Cohorts A and B	X[i]	X	—	—

	End of Treatment	Posttreatment		Survival Follow-up
	Within 7 Days After Last Dose of Study Treatment or EOT Decision	60-Day Follow-up Visit[a,b,c]	≤ 1 year from last dose[b]	≤ 1 year from last tumor lesion assessment[b,c,d]
Visit Window	**≤ 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**
Blood for PK assays[h] (GS-3583) – Randomized Expansion Cohorts A and B	Blood for PK Assays[h] (GS-3583) – Safety Run-in Cohorts A and B	X	—	—
Blood for PK assays[h] (zimberelimab) – Safety Run-in and Randomized Expansion Cohort A	X[i]	X	—	—
Blood for ADA assays[j]	X[i]	X	—	—
Biomarker Procedures/Assessments				
Whole blood for Pharmacodynamic Biomarkers (PBMC and plasma)[k]	X[i]	X	—	—
Whole blood for blood cell count[k]	X[i]	X	—	—
Whole blood for CHIP mutation analysis[k]	X	—	—	—
Whole blood for TCR sequencing[k]	X	—	—	—
Whole blood for circulating tumor DNA[k]	X	—	—	—
Whole blood for Paxgene RNA[k]	X	—	—	—
Serum pharmacodynamics for circulating factors[k]	X	—	—	—
Stool sample for microbiome sequencing[k]	X	—	—	—
CCI				
Overall survival[b,c,d]	—	—	—	X

ADA = antidrug antibody; AEs = adverse events; CHIP = clonal hematopoiesis of indeterminate potential; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; MUGA = multigated acquisition; PBMC = peripheral blood mononuclear cell; PE = physical exam; PK = pharmacokinetic(s); SAEs = serious adverse events; TCR = T-cell receptor

a All subjects who discontinue treatment will have a follow-up visit 60 days (± 7 days) after the last dose of study drug. Collect all AEs, regardless of cause or relationship, until 90 days after the last dose of study drug (Section 7.3).

b Subjects who discontinue treatment due to reasons other than progressive disease and/or start of a new line of anticancer therapy will complete the 60-day follow-up and continue tumor imaging assessments at the predefined schedule until documented progressive disease, initiation of a new anticancer therapy, or up to 1 year after the last dose of study drug, whichever occurs first; and then move into survival follow-up for up to 1 year after the completion/discontinuation of tumor lesion assessments

c Subjects who discontinue due to progressive disease and/or start of a new line of anticancer therapy will complete the 60-day follow-up and then enter the survival follow-up period for up to 1 year after the completion/discontinuation of tumor lesion assessments.

d During the survival follow-up period, subjects will be contacted by telephone to assess for survival status and any new malignancies every 3 months for up to 1 year after the completion/discontinuation of tumor lesion assessments. No imaging assessment is required for survival follow-up. Any new malignancies will be reported as SAEs.

e Vital signs will only be measured while subject is in sitting, semi-recumbent, or supine position.

f On-study imaging will be performed every 6 weeks from first treatment dose and will continue until progressive disease as assessed by the investigator, a new line of anticancer therapy is initiated, or up to 1 year after the last dose of study drug, whichever occurs first. For subjects who permanently discontinue from the study in the absence of progressive disease/or start of a new line of anticancer therapy and will not be continuing tumor imaging during the posttreatment period, additional imaging is recommended at the EOT visit if the last imaging was performed more than 30 days prior. For subjects that met progressive disease clinically, subjects will continue tumor imaging until progressive disease is confirmed radiographically or prior to the start of a new line of anticancer therapy. The timing of on-study treatment imaging should follow calendar days and should not be adjusted for delays in treatment administration or for visits.

g Urine pregnancy tests will be performed locally at each site. After the 60-day follow-up visit, urine pregnancy tests will be performed monthly until the end of the contraception requirement (Appendix 5).

h PK Assays: See details of all PK sample collections in Section 6.5.1.2, Table 6-4, and Table 6-5.

i Blood samples will only be collected at the EOT visit for subjects that terminate early from study treatment.

j ADA Assays: Assessed at the 60-day follow-up visit (approximately 60 days after the last dose of study drug). An additional blood sample will be collected at the EOT visit if a subject terminates early from study treatment.

k Biomarker Assays: See details on all biomarker sample collections in Section 6.5.2.1.

l CCI [redacted]

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a) Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless the subject is permanently sterile or has medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women < 54 years of age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b) Definition of Male Fertility

For the purposes of this study, a male born subject is considered fertile after the initiation of puberty unless the subject is permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception

GS-3583 is contraindicated in pregnancy as a malformation effect has been demonstrated/suspected or is unknown, taking into consideration class effects and/or a strong suspicion of human teratogenicity/fetotoxicity in early pregnancy based on nonclinical data.

For GS-3583, there is no anticipated PK interaction with progestin or other steroids based on the distinct clearance pathways. Refer to the latest version of the investigator's brochure (IB) for additional information.

Based on its mechanism of action and consistent with the risks identified for the approved anti-programmed cell death protein 1 (PD-1) agents, nivolumab and pembrolizumab, zimberelimab may cause fetal harm when administered to a pregnant woman. No contraindication to hormonal contraception is described in the zimberelimab IB. Refer to the latest version of the IB for additional information.

Based on the mechanism of action, 5-fluorouracil (5-FU) can cause fetal harm when administered to a pregnant woman. In animal studies, administration of 5-FU at doses lower than a human dose of 12 mg/kg caused teratogenicity. If this drug is used during pregnancy or if the subject becomes pregnant while taking this drug, the subject should be apprised of the potential hazard to a fetus. There is no contraindication to hormonal contraception according to the 5-FU prescribing information.

Based on human data from published literature, cisplatin for injection can cause fetal harm when administered to pregnant women. Data demonstrate transplacental transfer of cisplatin. Exposure of pregnant women to cisplatin-containing chemotherapy has been associated with oligohydramnios, intrauterine growth restriction, and preterm birth. Cases of neonatal acute respiratory distress syndrome, cytopenias, and hearing loss have been reported. Cisplatin for injection administration to animals during and after organogenesis resulted in teratogenicity. There is no contraindication to hormonal contraception according to the cisplatin prescribing information.

Based on the mechanism of action and findings in animals, docetaxel can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant during therapy with docetaxel. If the subject becomes pregnant while receiving docetaxel, the subject should be apprised of the potential hazard to the fetus. There is no contraindication to hormonal contraception according to the docetaxel prescribing information.

b) Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of < 1% per year. They must have a negative serum pregnancy test at screening and a negative urine pregnancy test at each Day 1 visit of every cycle prior to enrollment/study drug administration. Pregnancy tests will be performed at monthly intervals thereafter until 12 weeks after the last dose of study drug for subjects in Part 1 and until the end of the contraception requirement for subjects in Part 2.

Duration of required contraception for female subjects in this clinical study should start from Screening visit until 6 months after last dose of study drug unless there is a longer time requirement described in the country-specific prescribing information. If the duration of contraception differs by study drug, the longest effective duration of contraception should be observed.

Female subjects must agree to one of the following contraceptive methods:

Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

Or

Consistent and correct use of 1 of the following methods of birth control listed below:

- Non-hormonal intrauterine device (IUD)
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

Or

Female subjects of childbearing potential who wish to use a hormonally based method must use it in conjunction with a barrier method, preferably a male condom. Hormonal methods are restricted to those associated with the inhibition of ovulation. Hormonally based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods (each method must be used with a barrier method, preferably male condom)
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring
  - Subdermal contraceptive implant
  - Hormonal intrauterine device (IUD)
- Barrier methods (each method must be used with a hormonal method)
  - Male condom (with or without spermicide)
  - Female condom (with or without spermicide)
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Sponge with spermicide

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraceptive requirement. If needed, female subjects of childbearing

potential should be advised to seek advice about egg donation and cryopreservation of germ cells before treatment.

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration of study drug may be achieved in a female partner from exposure of the male subject's seminal fluid and poses a potential risk to an embryo/fetus. Male subjects with female partners of childbearing potential must use condoms during treatment and until 6 months after last dose of study drug unless there is a longer time requirement described in the country-specific prescribing information. If the duration of contraception differs by study drug, the longest effective duration of contraception should be observed. If the female partner of childbearing potential is not pregnant, additional contraception recommendations should also be considered.

Male subjects must also refrain from sperm donation during treatment and until the end of contraceptive requirement. If needed, male subjects should be advised to seek advice about sperm donation and cryopreservation of germ cells before treatment.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Female subjects will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study to 6 months after last study drug dose. Study drug must be discontinued immediately.

Male subjects whose partner has become pregnant or suspects she is pregnant from start of study to 6 months of last the study drug dose must also report the information to the investigator.

Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.4.2.3.

Appendix 6. NCI CTCAE v5.0 Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Appendix 7. Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1)

Measurability of tumor at baseline

Definitions: At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by computed tomography (CT) scan (CT scan slice thickness no greater than 5 mm).

10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and at follow-up, only the short axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable: All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Bone lesions:

Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or magnetic resonance imaging (MRI) can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic lesions:

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subjects, these are preferred for selection as target lesions.

Lesions with prior local treatment:

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only one or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Tumor response evaluation

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 diameters of target lesions, taking as reference the baseline sum diameters.

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

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

Evaluation of non-target lesions

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

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

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

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Also refer to Section 3.4.1 of the protocol for additional information regarding treatment beyond initial progressive disease.

Table 11-1. Time Point Response: Subjects with Target (+/- Non-target) Disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-progressive disease	No	PR
CR	Not evaluated	No	PR
PR	Non-progressive disease or not all evaluated	No	PR
SD	Non-progressive disease or not all evaluated	No	SD
Not all evaluated	Non-progressive disease	No	NE
Progressive disease	Any	Yes or No	Progressive disease
Any	Progressive disease	Yes or No	Progressive disease
Any	Any	Yes	Progressive disease

CR = complete response; PR = partial response; SD = stable disease; NE = not evaluable

Table 11-2. Time Point Response: Subjects with Non-target Disease Only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-progressive disease	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal progressive disease	Yes or No	Progressive disease
Any	Yes	Progressive disease

CR = complete response; NE = not evaluable

a 'Non-CR/non-PD' is preferred over 'SD' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some studies so to assign this category when no lesions can be measured is not advised.

Prot GS-US-496-5657 amd-2

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	19-Apr-2022 00:41:40