CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2 Study of Magrolimab Combination Therapy in Patients With Unresectable, Locally Advanced or Metastatic Triple-Negative Breast Cancer
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number:	154653
EudraCT Number:	2021-001074-27
Clinical Trials.gov Identifier:	NCT04958785
Indication:	Triple-Negative Breast Cancer
Protocol ID:	GS-US-586-6144
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 04 March 2021 Amendment 1: 13 April 2021 Amendment 1.1-VHP: 18 October 2021 Amendment 2: 15 December 2021 Amendment 3: 27 January 2022 Amendment 1.2-UK: 03 February 2022 Amendment 3.1-UK: 17 March 2022 Amendment 3.1-KOR: 31 October 2022 Amendment 3.2-KOR: 01 February 2023 Amendment 4: 07 March 2023 Amendment 5: 30 October 2023 Amendment 6: 30 January 2024

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

Gilead Sciences, Inc.
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Study Title:	A Phase 2 Study of Magrolimab Combination Therapy in Patients With Unresectable, Locally Advanced or Metastatic Triple-Negative Breast Cancer
IND Number:	154653
EudraCT Number:	2021-001074-27
Clinical Trials.gov Identifier:	NCT04958785
Study Centers Planned:	Approximately 50 centers

Objectives and Endpoints:

Primary Objectives	Primary Endpoints
Safety Run-in Cohort 1: • To evaluate the safety, tolerability, and recommended Phase 2 dose (RP2D) of magrolimab in combination with nab-paclitaxel or paclitaxel Phase 2 Cohort 1: • To compare the efficacy of magrolimab in combination with nab-paclitaxel or paclitaxel versus nab-paclitaxel or paclitaxel alone as determined by progression-free survival (PFS) by investigator assessment Safety Run-in Cohort 2: • To evaluate the safety, tolerability, and RP2D of magrolimab in combination with sacituzumab govitecan Cohort 2 (Safety Run-in Cohort 2 and Phase 2 Cohort 2): • To evaluate the efficacy of magrolimab in combination with sacituzumab govitecan as determined by confirmed objective response rate (ORR) by investigator assessment	Safety Run-in Cohorts 1 and 2: • Incidence of dose-limiting toxicities (DLTs), adverse events (AEs), and laboratory abnormalities according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 Phase 2 Cohort 1: • PFS, defined as the time from the date of randomization until the earliest date of documented disease progression as determined by investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, or death from any cause, whichever occurs first Cohort 2 (Safety Run-in Cohort 2 and Phase 2 Cohort 2): • Confirmed ORR (defined as the proportion of patients who achieve complete response or partial response that is confirmed at least 4 weeks after initial documentation of response), as determined by investigator assessment per RECIST, Version 1.1

Secondary Objectives	Secondary Endpoints
Phase 2 Cohort 1: • To compare the efficacy between treatment arms by ORR by investigator assessment • To compare the efficacy between treatment arms by additional measures of efficacy, including duration of response (DOR) and overall survival (OS) • To compare the safety and tolerability between treatment arms Cohort 2 (Safety Run-in Cohort 2 and Phase 2 Cohort 2): • To evaluate PFS by investigator assessment • To evaluate additional measures of efficacy of magrolimab in combination with sacituzumab govitecan, including DOR and OS • Safety and tolerability of magrolimab in combination with sacituzumab govitecan Safety Run-in Cohorts 1 and 2 and Phase 2 Cohorts 1 and 2: • To evaluate the pharmacokinetics (PK) and immunogenicity of magrolimab in combination with anticancer chemotherapies	Phase 2 Cohort 1 and Cohort 2 (Safety Run-in Cohort 2 and Phase 2 Cohort 2): • Confirmed ORR, as determined by investigator assessment per RECIST, Version 1.1 (only for Phase 2 Cohort 1) • PFS, as determined by investigator assessment per RECIST, Version 1.1, or death from any cause, whichever occurs first (only for Cohort 2) • DOR, defined as time from first documentation of complete response or partial response to the earliest date of documented disease progression as determined by investigator assessment, per RECIST, Version 1.1, or death from any cause, whichever occurs first • OS, defined as time from date of randomization to death from any cause • Incidence of AEs and laboratory abnormalities according to NCI CTCAE, Version 5.0 Safety Run-in Cohorts 1 and 2 and Phase 2 Cohorts 1 and 2: • Magrolimab concentration versus time and antidrug antibodies (ADA) to magrolimab

[redacted]

Study Design:

This is a Phase 2, randomized (Phase 2 Cohort 1 only), open-label, multicenter study to evaluate magrolimab in combination with either nab-paclitaxel or paclitaxel for patients with untreated, unresectable, locally advanced or metastatic triple-negative breast cancer (mTNBC) and magrolimab in combination with sacituzumab govitecan for patients with unresectable, locally advanced or mTNBC who have received at least 1 and no more than 2 prior lines of treatment in the advanced setting. This study will consist of 2 Safety Run-in Cohorts:

- **Safety Run-in Cohort 1:** magrolimab in combination with choice of nab-paclitaxel or paclitaxel in patients previously untreated for unresectable, locally advanced or mTNBC whose tumors are not appropriate for immune checkpoint inhibitor therapy

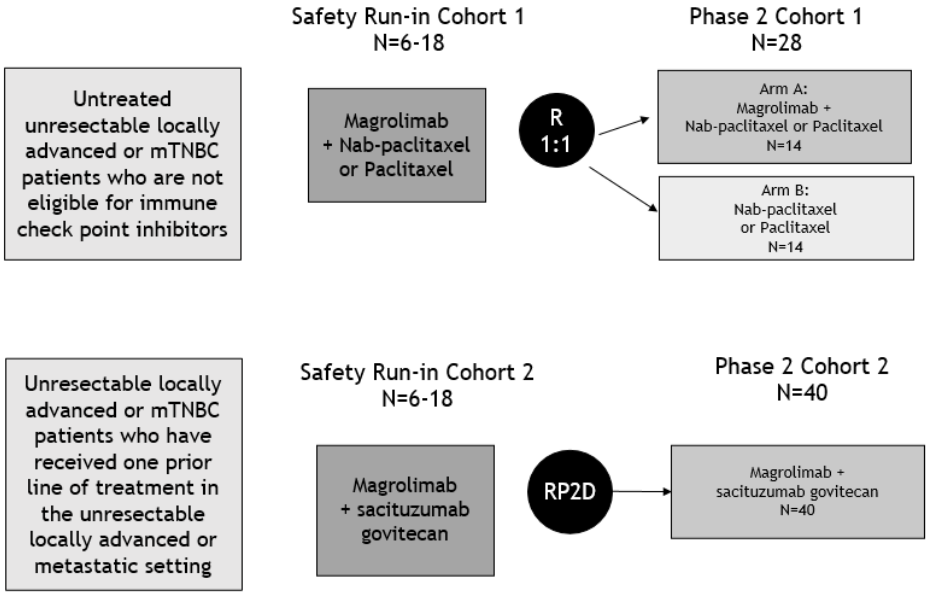
After completion of Safety Run-in Cohort 1, Phase 2 Cohort 1 will be open to enrollment.

- **Phase 2 Cohort 1:** a randomized, open-label cohort of magrolimab in combination with choice of nab-paclitaxel or paclitaxel (Experimental Arm A) versus nab-paclitaxel or paclitaxel (Control Arm B) in patients previously untreated for unresectable, locally advanced or mTNBC whose tumors are not appropriate for immune checkpoint inhibitor therapy.
- **Safety Run-in Cohort 2:** magrolimab in combination with sacituzumab govitecan in patients with unresectable, locally advanced or mTNBC who have received at least 1 and no more than 2 prior lines of treatment in the unresectable, locally advanced or metastatic setting.

After completion of Safety Run-in Cohort 2, Phase 2 Cohort 2 will be open to enrollment.

- **Phase 2 Cohort 2**: magrolimab in combination with sacituzumab govitecan in patients with unresectable, locally advanced or mTNBC who have received at least 1 and no more than 2 prior lines of treatment in the unresectable, locally advanced or metastatic setting.

The study schematic is provided below.



mTNBC = metastatic triple-negative breast cancer; N = number of patients; R = ratio; RP2D = recommended Phase 2 dose

Safety Run-in Cohort 1 and Safety Run-in Cohort 2: Initially, up to 6 patients will be enrolled in each Safety Run-in Cohort at a starting dose level. A DLT evaluation period of 1 cycle (28 days) for Cohort 1 and (21 days) for Cohort 2 will occur.

Even though no dose-dependent toxicities have been observed with magrolimab, in order to preserve the efficacious doses of the combination partner drugs, dose de-escalation will take place for magrolimab. Dose de-escalation decisions will be made as follows:

- If 2 or less of 6 DLT-evaluable patients experience a DLT in Cycle 1, enrollment into Phase 2 Cohort 1 or Phase 2 Cohort 2 may begin at this dose level as the RP2D.
- If more than 2 patients experience at least one DLT during Cycle 1, enrollment at the current dose level will immediately stop and dose de-escalation will occur. Up to another 6 patients will then be enrolled and evaluated at a lower dose level in the same manner.

Approximately 18 patients (each cohort) could be potentially enrolled and evaluated during the Safety Run-in Cohorts.

DLT Assessment Period for Safety Run-in Cohort 1: The DLT assessment period will be the first cycle (28 days). Patients are considered evaluable for assessment of a DLT if either of the following criteria is met in the DLT assessment period:

- The patient experienced a DLT at any time after initiation of the first infusion of magrolimab.

- The patient did not experience a DLT and completed at least 3 infusions of magrolimab (28-day cycle), and at least 2 doses of nab-paclitaxel or paclitaxel in Safety Run-in Cohort 1.

DLT Assessment Period for Safety Run-in Cohort 2: The DLT assessment period will be the first cycle (21 days). Patients are considered evaluable for assessment of a DLT if either of the following criteria is met in the DLT assessment period:

- The patient experienced a DLT at any time after initiation of the first infusion of magrolimab.
- The patient did not experience a DLT and completed at least 2 infusions of magrolimab (21-day cycle), and at least 2 infusions of sacituzumab govitecan in Safety Run-in Cohort 2.

If a patient experiences a DLT during the DLT assessment period, the patient will discontinue treatment.

Patients who are not evaluable for DLT assessment in the Safety Run-in Cohorts will be replaced.

The DLT definition is provided in the main protocol (Section 3.1.1.2).

Phase 2 Cohort 1: Once Safety Run-in Cohort 1 is completed and the RP2D for magrolimab in combination with either nab-paclitaxel or paclitaxel is determined, the sponsor will open Phase 2 Cohort 1. In this open-label, randomized, 2-arm cohort, unresectable, locally advanced or mTNBC patients will be randomized in a 1:1 ratio to receive either magrolimab in combination with the choice of nab-paclitaxel or paclitaxel (Experimental Arm A) or nab-paclitaxel or paclitaxel (Control Arm B). The primary efficacy assessment will be investigator-assessed PFS. In the original study design, the primary analysis was to occur after 63 events; however, due to the early closure of Phase 2 Cohort 1, the primary analysis will occur when every enrolled patient has a minimum of 6 months follow-up. Stratification factors for randomization include the following: 1) receipt versus nonreceipt of neoadjuvant and/or adjuvant taxane therapy, 2) presence versus absence of liver metastases, 3) treatment with nab-paclitaxel versus paclitaxel.

Phase 2 Cohort 2: Once Safety Run-in Cohort 2 is completed and the RP2D for magrolimab in combination with sacituzumab govitecan is determined, the sponsor will open Phase 2 Cohort 2. In this open-label single-arm cohort, unresectable, locally advanced or mTNBC patients will receive magrolimab in combination with sacituzumab govitecan. The primary efficacy assessment will be investigator-assessed confirmed ORR.

Number of Patients Planned:	Approximately 104 patients total • Safety Run-in Cohort 1: approximately 6 to 18 patients • Phase 2 Cohort 1: approximately 28 patients • Safety Run-in Cohort 2: approximately 6 to 18 patients • Phase 2 Cohort 2: approximately 40 patients
Target Population:	**Phase 2 Cohort** 1: Previously untreated patients with unresectable, locally advanced or mTNBC whose tumors are not appropriate for immune checkpoint inhibitor therapy who do not express programmed death ligand 1 (PD-L1), as determined by an approved test according to local standards. **Phase 2 Cohort 2**: Patients with unresectable locally advanced or mTNBC who have received at least 1 and no more than 2 prior lines of treatment in the unresectable, locally advanced or metastatic setting.
Duration of Treatment:	**Cohort 1**: Cycle lengths are 28 days. All patients will continue study treatment unless they meet study treatment discontinuation criteria. **Cohort 2**: Cycle lengths are 21 days. All patients will continue study treatment unless they meet study treatment discontinuation criteria.
Diagnosis and Main Eligibility Criteria:	**Inclusion Criteria:** All patients must meet all of the following inclusion criteria to be eligible for participation in this study: 1) Patient has provided informed consent. 2) Patient is willing and able to comply with clinic visits and procedures outlined in the study protocol. 3) Male or female, at least 18 years of age. 4) Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 5) Laboratory measurements, blood counts: a) Hemoglobin must be ≥ 9 g/dL prior to initial dose of study treatment. Red blood cell (RBC) transfusions are allowed to meet hemoglobin eligibility within limits set per Exclusion Criterion #4, except in South Korea. b) Absolute neutrophil count at least 1.5×10^9/L without growth factor support within 2 weeks of study treatment initiation. c) Platelets at least 100×10^9/L.

6) Laboratory measurements, renal function:
   a) Patients must have adequate renal function as demonstrated by a creatinine clearance of at least 30 mL/min; calculated by the Cockcroft Gault formula.
7) Adequate liver function, as demonstrated by:
   a) Aspartate aminotransferase less than or equal to 2.5 × upper limit of normal (ULN) or less than or equal to 5 × ULN in patients with liver metastases.
   b) Alanine aminotransferase less than or equal to 2.5 × ULN or less than or equal to 5 × ULN in patients with liver metastases.
   c) Bilirubin less than or equal to 1.5 × ULN, or less than or equal to 3.0 × ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or genetic equivalent.
8) Pretreatment blood cross-match completed.
9) Male and female patients of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 5.
10) Measurable disease according to RECIST, Version 1.1. Previously irradiated lesions can be considered as measurable disease only if disease progression has been unequivocally documented at that site since radiation.
11) Patients must have a life expectancy of 3 months or greater, in the opinion of the investigator.

Safety Run-in Cohort 1 and Phase 2 Cohort 1

In addition to meeting the inclusion criteria for all patients, patients who are enrolled into Safety Run-in Cohort 1 and Phase 2 Cohort 1 must fulfill the following cohort-specific inclusion criteria:

12) Patients previously untreated with systemic therapy for unresectable locally advanced or metastatic breast cancer and with a diagnosis of TNBC that is histologically or cytologically confirmed based on the most recent analyzed biopsy or other pathology specimen, defined as negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) according to the most recent American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guideline (Appendix 9).
13) Patients whose tumors are considered PD-L1 negative, as determined by an approved test according to local standards.
14) Prior systemic treatment for neoadjuvant and/or adjuvant therapy and/or curative intent radiation therapy is permitted if completed at least 6 months prior to enrollment.

Note: Maintenance therapies are not counted as separate lines of therapy.

Safety Run-in Cohort 2 and Phase 2 Cohort 2

In addition to meeting the inclusion criteria for all patients, patients who are enrolled into Safety Run-in Cohort 2 and Phase 2 Cohort 2 must fulfill the following cohort-specific inclusion criteria:

15) Patients with unresectable, locally advanced or metastatic breast cancer with a diagnosis of TNBC that is histologically or cytologically confirmed based on the most recent analyzed biopsy or other pathology specimen, defined as negative for ER, PR, and HER2 according to the most recent ASCO/CAP guideline (Appendix 9), who have received at least 1 and no more than 2 prior lines of systemic therapy in the unresectable, locally advanced/metastatic setting. Patients must have been previously treated with a taxane in the neoadjuvant, adjuvant, or locally advanced/metastatic setting.

16) Patients with tumors considered positive for PD-L1 expression (as determined by an approved test according to local standards) must have received an immune checkpoint inhibitor for a prior line of treatment for locally advanced/metastatic disease.

Exclusion Criteria:

Patients who meet *any* of the following exclusion criteria are not to be enrolled in this study:

1) Positive serum pregnancy test.
2) Breastfeeding female.
3) Active central nervous system (CNS) disease. Patients with asymptomatic and stable, treated CNS lesions who have been off steroids, radiation and/or surgery, and/or other CNS-directed therapy for at least 4 weeks are allowed.
4) RBC transfusion dependence, defined as requiring more than 2 units of packed RBC transfusions during the 4-week period prior to screening. RBC transfusions are permitted during the screening period and prior to enrollment to meet the hemoglobin inclusion criteria, except in South Korea.
5) History of hemolytic anemia, autoimmune thrombocytopenia, or Evans syndrome in the last 3 months.
6) Known hypersensitivity to any of the study drugs, the metabolites, or formulation excipient.
7) Prior treatment with CD47 or signal regulatory protein alpha-targeting agents.

8) Current participation in another interventional clinical study. Patients enrolled in a clinical study who are no longer receiving therapeutic intervention are eligible.
9) Known inherited or acquired bleeding disorders.
10) Significant disease or medical conditions, as assessed by the investigator and sponsor, that would substantially increase the risk-benefit ratio of participating in the study. This includes, but is not limited to, acute myocardial infarction within the last 6 months, unstable angina, uncontrolled diabetes mellitus, significant active infections, and congestive heart failure New York Heart Association Class III-IV. Additional information for sites in the United Kingdom (UK) is provided in Appendix 12.
11) Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancies for which patients are not on active anticancer therapies and who are in complete remission for over 2 years.
12) Known active or chronic hepatitis B or C infection or human immunodeficiency virus infection in medical history.
13) Uncontrolled pleural effusion.
14) Uncontrolled hypercalcemia (Grade 2 or higher) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy.
15) Rapid deterioration during screening prior to enrollment (eg, significant change in performance status, 20% or greater decrease in serum albumin levels or uncontrolled tumor-related pain).
16) Severe/serious systemic infection within 4 weeks of randomization or any active, uncontrolled infection requiring systemic therapy within 7 days of enrollment.
17) Other concurrent medical or psychiatric conditions that, in the investigator's opinion, may be likely to confound study interpretation or prevent completion of study procedures and follow-up examinations.
18) Prior anticancer therapy within the specified timeframes prior to start of magrolimab is not permitted: 2 weeks for chemotherapy agents, endocrine therapy, or targeted small molecule therapy; 3 weeks for monoclonal antibodies, antibody-drug conjugates, immunotherapy, or investigational agents.
19) Patients who have received a live vaccine within 30 days of randomization.

	Safety Run-in Cohort 1 and Phase 2 Cohort 1 Patients who meet the following exclusion criterion are not eligible to be enrolled into Safety Run-in Cohort 1 or Phase 2 Cohort 1: 20) Disease progression within 6 months following neoadjuvant/adjuvant therapy or prior lines of systemic therapy for unresectable locally advanced or metastatic breast cancer. NOTE: Localized non-CNS radiotherapy, hormonal therapy for breast cancer in the curative setting, and treatment with bisphosphonates and receptor activator of nuclear factor kappa B ligand inhibitors are not included in Exclusion Criterion #20. Patients should be recovered from the effects of radiation. Additional information for sites in the UK is provided in Appendix 12. Safety Run-in Cohort 2 and Phase 2 Cohort 2 Patients who meet *any* of the following exclusion criteria are not eligible to be enrolled into Safety Run-in Cohort 2 or Phase 2 Cohort 2: 21) Patients with active chronic inflammatory bowel disease (ulcerative colitis, Crohn disease) and patients with a history of bowel obstruction or gastrointestinal perforation within 6 months of enrollment. 22) Patients who previously received topoisomerase I inhibitors or antibody-drug conjugates containing a topoisomerase inhibitor. 23) High-dose systemic corticosteroids (≥ 20 mg of prednisone or its equivalent) are not allowed within 2 weeks of Cycle 1 Day 1. 24) Have not recovered (ie, ≥ Grade 2 is considered not recovered) from AEs due to a previously administered agent — Note: patients with any grade of neuropathy, alopecia, hypo- or hyperthyroidism, or other endocrinopathies that are well controlled with hormone replacement are an exception to this criterion and will qualify for the study. — Note: if patients received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy. NOTE: Localized non-CNS radiotherapy is not criteria for exclusion. Patients should be recovered from the effects of radiation.
Study Procedures/ Frequency:	Refer to Appendix Table 1, Appendix Table 2, and Appendix Table 3.

Test Product, Dose, and Mode of Administration:	Safety Run-in Cohort 1 Starting Doses: • Magrolimab 1 mg/kg intravenous (IV) (priming) • Magrolimab 30 mg/kg IV every week for the first 2 cycles and magrolimab 30 mg/kg IV every 2 weeks for Cycle 3 and onward In combination with nab-paclitaxel 100 mg/m^2 IV or paclitaxel 90 mg/m^2 IV per investigator discretion. Experimental Arm A of Phase 2 Cohort 1: Magrolimab dose will be determined in Safety Run-in Cohort 1. In combination with nab-paclitaxel 100 mg/m^2 IV or paclitaxel 90 mg/m^2 IV per investigator discretion. Safety Run-in Cohort 2 Starting Doses: • Magrolimab 1 mg/kg IV (priming) • Magrolimab 30 mg/kg IV every week for the first 2 cycles and magrolimab 60 mg/kg IV every 3 weeks for Cycle 3 and onward In combination with sacituzumab govitecan 10 mg/kg IV. Phase 2 Cohort 2: Magrolimab dose will be determined in Safety Run-in Cohort 2. In combination with sacituzumab govitecan 10 mg/kg IV.
Reference Therapy, Dose, and Mode of Administration	Control Arm B of Phase 2 Cohort 1: Nab-paclitaxel 100 mg/m^2 IV or paclitaxel 90 mg/m^2 IV per investigator discretion
Criteria for Evaluation:	
Safety:	Safety will be evaluated by data including the incidence of AEs for the duration of the study, assessment of clinical laboratory test findings, physical examination, 12-lead electrocardiogram, ECOG performance status, and vital signs measurements. Adverse events will be graded using NCI CTCAE, Version 5.0.
Efficacy:	**Cohort 1 (Phase 2 only)**: Efficacy will be evaluated by PFS, ORR, DOR, OS, and PRO assessment (EORTC-QLQ-C30, EORTC-QLQ-BR23, and EQ-5D-5L) scores. Assessment of response will be measured by RECIST, Version 1.1. **Cohort 2**: Efficacy will be evaluated by PFS, ORR, DOR, and OS. Assessment of response will be measured by RECIST, Version 1.1.

Pharmacokinetics:	Magrolimab serum drug concentrations will be assessed at predose at multiple time points until study discontinuation. Peripheral blood for immunogenicity assessments for ADA against magrolimab will also be collected at predose and multiple time points during the study.
Statistical Methods:	Analysis Data Sets The DLT-Evaluable Analysis Set for Safety Run-in Cohort 1 will include all patients who meet 1 of the following criteria in the DLT assessment period: • Patient experienced a DLT at any time after initiation of the first infusion of magrolimab. • Patient did not experience a DLT and completed at least 3 infusions of magrolimab (28-day cycle) and at least 2 doses of nab-paclitaxel or paclitaxel in Safety Run-in Cohort 1. The DLT-Evaluable Analysis Set for Safety Run-in Cohort 2 will include all patients who meet 1 of the following criteria in the DLT assessment period: • Patient experienced a DLT at any time after initiation of the first infusion of magrolimab. • Patient did not experience a DLT and completed at least 2 infusions of magrolimab (21-day cycle) and at least 2 infusions of sacituzumab govitecan in Safety Run-in Cohort 2. For Safety Run-in Cohorts, the modified Intent-to-Treat (ITT) Analysis Set will include all patients who received at least 1 dose of any study drug and the Safety Analysis Sets will include all patients who received at least 1 dose of any study drug. For Phase 2 Cohort 1, the ITT Analysis Set will include all randomized patients according to the treatment arm to which the patients are randomized, unless otherwise specified. The Safety Analysis Set will include all randomized patients who received at least 1 dose of any study treatment, with treatment assignments designated according to the actual treatment received. For Phase 2 Cohort 2, the Safety Analysis Set will include all patients who received at least 1 dose of any study drug. For Cohort 2 (Safety Run-in Cohort 2 and Phase 2 Cohort 2), the modified ITT Analysis Set will include all patients who received at least 1 dose of study drug at the selected Phase 2 Cohort 2 dose level. The PK Analysis Set will include all patients who received any amount of magrolimab and have at least 1 measurable posttreatment serum concentration of magrolimab.

The Immunogenicity Analysis Set will include all patients who received any amount of magrolimab and had at least 1 evaluable anti-magrolimab antibody test result.

The Biomarker Analysis Set includes all patients who received any study drug and have at least 1 evaluable biomarker measurement available. This will be the primary analysis set for all biomarker data analyses.

Dose-Determination Analysis

For the purposes of making the dose de-escalation decisions for Safety Run-in Cohort 1 and 2, dose-determination analyses of relevant safety data focusing on DLTs and overall safety profile will be conducted by the sponsor after all patients have completed the required DLT assessment period as specified in Section 3.1.1. Safety assessments (eg, AEs, electrocardiogram, laboratory results) will be displayed to facilitate the dose de-escalation decisions.

Efficacy Analysis

For Phase 2 Cohort 1, PFS by investigator assessment will be analyzed using Kaplan-Meier (KM) methods. Patients who did not have documented disease progression or death will be censored at the date of their last adequate response assessment during the study with documentation of no disease progression. The KM estimate of the survival function will be computed, and the results will be presented using KM curves. The median will be provided along with the corresponding 95% CI. A log-rank test may be used to compare treatment difference in PFS. A Cox proportional hazard regression model may be used to estimate the hazard ratio (HR) and its 2-sided 95% CI.

For Safety Run-in Cohort 2 and Phase 2 Cohort 2, confirmed ORR by investigator assessment with 95% CI based on the Clopper-Pearson method will also be estimated. Patients who do not have sufficient baseline or on-study tumor assessment to characterize response will be counted as nonresponders.

Safety Analysis

Safety will be assessed via AEs, clinical laboratory tests, and concomitant medications in the Safety Analysis Set. Information regarding study drug administration, study drug compliance, and other safety variables will also be summarized.

Sample Size Calculation

Based on the original design for Phase 2 Cohort 1, using an unstratified log-rank test, a total of 63 PFS events provides 82% power at a 1-sided alpha of 0.15 to detect a HR of 0.61 (assuming median PFS of at least 9 months compared to a control arm median PFS of 5.5 months).

Assuming an accrual period of 15 months, a minimum follow-up time of 6 months, and a 5% annual drop-out rate, 92 total patients (46 patients per arm) would be required to obtain 63 events.

Due to the early closure of Phase 2 Cohort 1, 28 patients have been enrolled and randomized for Arm A and Arm B. The analysis of the PFS given the current sample size is under powered and will be descriptive only.

For Safety Run-in Cohort 2 and Phase 2 Cohort 2, using chi-square test, a total of 46 patients (including 6 patients in Safety Run-in Cohort 2 and 40 in Phase 2 Cohort 2) provides 88% power at a 1-sided alpha of 0.15 to detect an ORR of 50% compared with a null ORR of 34%.

Power calculations were performed using EAST 6.5.

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

5F9	magrolimab
1L	first-line
ABO	any of the 4 blood groups A, B, AB, and O comprising the ABO system
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
CAP	College of American Pathologists
CD47	cluster of differentiation 47
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CPS	Combined Positive Score
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAT	direct antiglobulin test
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire
EORTC-QLQ BR23	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire–Breast Cancer Module
EOT	end of treatment
EQ-5D	EuroQol (5 dimensions)

EQ-5D-5L	5-level EuroQol 5 dimensions
EQ-VAS	EuroQol visual analogue scale
ER	estrogen receptor
EU	European Union
Fc	crystallizable fragment
FDA	Food and Drug Administration
G-CSF	granulocyte-colony stimulating factor
GDRC	Gilead Data Review Committee
Gilead	Gilead Sciences
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
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
IgG4	immunoglobulin G 4
IND	investigational new drug
IRB	institutional review board
IRR	infusion-related reaction
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous
K_D	dissociation constant
KM	Kaplan-Meier
mAb	monoclonal antibody
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTNBC	metastatic triple-negative breast cancer
nab	nanoparticle albumin-bound
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)

PD-L1	programmed cell death ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	progesterone receptor
PRO	patient-reported outcome
PS	Patient Safety
r/r	relapsed/refractory
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RO	receptor occupancy
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SIRPα	signal regulatory protein alpha
SOP	standard operating procedure
SRT	safety review team
SSRs	special situation reports
SUSAR	suspected unexpected serious adverse reaction
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TNBC	triple-negative breast cancer
Trop-2	trophoblast cell-surface antigen 2
UK	United Kingdom
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
w/v	weight-to-volume ratio

1. INTRODUCTION

1.1. Background

1.1.1. Background on Triple-Negative Breast Cancer

Triple-negative breast cancer (TNBC) is defined by the absence of immunostaining for estrogen receptor, progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Approximately 15% to 20% of all breast cancers are classified as TNBC. Generally, compared to other breast cancer subtypes, TNBC typically has more aggressive features, including a faster proliferation rate and a more invasive phenotype. Patients with locally advanced or metastatic TNBC (mTNBC) have a poor prognosis. Standard-of-care therapy for patients with mTNBC is chemotherapy. Taxane-based chemotherapeutic regimens are considered standard of care in first-line (1L) therapy for patients with mTNBC {Cardoso 2012}, with single-agent taxanes as the recommended chemotherapy regimen across international guidelines. However, even with these agents, the median overall survival (OS) is approximately 18 months or less {Cardoso 2020, Gradishar 2020}.

Taxane treatment can involve paclitaxel, nanoparticle albumin-bound (nab)paclitaxel, and docetaxel. While these 3 agents fall into the same taxane chemotherapeutic class, there are differences in terms of their safety profile, particularly between paclitaxel or nab-paclitaxel and docetaxel. Docetaxel has been associated with a more severe toxicity profile than paclitaxel or nab-paclitaxel, as well as a strict requirement for steroid premedication that cannot be tapered during the entire length of its administration. Nab-paclitaxel, which is an albumin-bound formulation of paclitaxel, was developed to avoid toxicities associated with administration of paclitaxel delivery-solution vehicles. Initial studies of nab-paclitaxel demonstrated higher antitumor activity as compared to paclitaxel in metastatic breast cancer. However, growing evidence suggests that paclitaxel and nab-paclitaxel may have a comparable benefit. Specifically, a study of the combination of paclitaxel or nab-paclitaxel with bevacizumab as 1L treatment for metastatic breast cancer, including mTNBC, was shown to provide similar progression-free survival (PFS) when given on a weekly basis {Rugo 2015}.

Moreover, results from the recent Phase 3 KEYNOTE 355 study evaluating pembrolizumab with a choice of chemotherapy in patients with previously untreated, locally recurrent, inoperable or metastatic TNBC whose tumors expressed programmed cell death ligand 1 (PD-L1) indicate generally a consistent benefit with regard to PFS irrespective of chemotherapy partner (including nab-paclitaxel or paclitaxel). The combinations were well tolerated, with no new safety concerns ({Cortes 2020}, {Cortes 2020}NCT02819518). In patients with a high-level of PD-L1 expression (Combined Positive Score [CPS] of at least 10) treated with pembrolizumab + nab-paclitaxel versus placebo + nab-paclitaxel, PFS was 9.9 versus 5.5 months, with a hazard ratio (HR [95% CI]) of 0.57 (0.34-0.95), and 9.6 versus 3.6 months (HR: 0.33; 85% CI: 0.14-0.76) with pembrolizumab + paclitaxel versus placebo+ paclitaxel. The addition of pembrolizumab to chemotherapy significantly improved the median OS in patients with a CPS of at least 10 as compared to chemotherapy alone (23.0 months vs 16.1 months, respectively) at a median follow-up of 44.1 months {Cortes 2021}. The pembrolizumab combination reduced the risk of death by

27% (HR: 0.73; 95% CI: 0.55-0.95; $P = 0.0093$). These results have served as the basis of pembrolizumab's approval in patients with locally recurrent unresectable or mTNBC whose tumors express PD-L1 (CPS of at least 10) {Cortes 2020}.

Additional immune checkpoint inhibitor combinations with taxanes are being evaluated in the mTNBC setting. Efficacy to date has been observed in the PD-L1–positive setting; however, therapeutic advances including novel combinations are needed for patients whose tumors do not express PD-L1.

Patients with TNBC who have failed approved or accepted treatments in the first- and second-line setting remain in dire need of additional therapeutic approaches. The trophoblast cell-surface antigen 2 (Trop-2) antigen is highly expressed on most solid epithelial cancers, including TNBC. Sacituzumab govitecan is a Trop-2 targeted antibody with camptothecin-derived agent SN-38, a topoisomerase I inhibitor, as its payload that binds to Trop-2 for targeted delivery of SN-38 directly to the tumor cell while minimizing systemic exposure of SN-38 to decrease host toxicity. Results from the ASCENT study evaluating sacituzumab govitecan monotherapy in patients with locally advanced or mTNBC who had relapsed after at least 2 prior chemotherapies for breast cancer (1 of which could be in the neoadjuvant/adjuvant setting provided progression occurred within a 12-month period) showed benefit with regards to PFS against single-agent chemotherapy. Patients treated with sacituzumab govitecan had a median PFS of 5.6 months versus 1.7 months in the single-agent chemotherapy. The study also showed an improved OS of 12.1 months in the sacituzumab govitecan arm versus 6.7 months in the chemotherapy arm {Bardia 2021}. The results of this study led to the approval of sacituzumab govitecan in patients with unresectable locally advanced or mTNBC who have received 2 or more prior systemic therapies, at least 1 of them for metastatic disease.

1.2. Magrolimab

1.2.1. General Information

Cluster of differentiation 47 (CD47) is a key molecule mediating cancer cell evasion of innate immune surveillance. CD47 expression is a well-characterized mechanism by which cancer cells, including cancer stem cells, overcome phagocytosis due to intrinsic expression of prophagocytic "eat me" signals {Jaiswal 2009, Majeti 2009}. The progression from normal cell to cancer cell involves changes in genes and gene expression that trigger programmed cell death and programmed cell removal {Chao 2012}. Many of the steps in cancer progression subvert the multiple mechanisms of programmed cell death, and the expression of the dominant antiphagocytic signal, CD47, may represent an important checkpoint {Chao 2012}. Increased CD47 expression was identified first on leukemic stem cells in human acute myeloid leukemia (AML) {Majeti 2009}, and since then it has been found that CD47 expression is increased on the surface of cancer cells in a diverse set of human tumor types.

In mouse xenograft models, CD47-blocking monoclonal antibodies (mAbs) inhibit human xenograft tumor growth and metastasis by enabling the phagocytosis and elimination of cancer cells from various hematologic malignancies and solid tumors {Chao 2011a, Chao 2010a, Chao 2011b, Edris 2012, Kim 2012, Majeti 2009, Willingham 2012}. Binding of CD47 expressed by

cancer cells to its ligand, signal regulatory protein alpha (SIRPα), expressed on phagocytes leads to inhibition of tumor cell phagocytosis. Thus, blockade of the CD47 SIRPα-signaling pathway by an anti-CD47 antibody leads to phagocytosis and elimination of tumor cells. Selective targeting of tumor cells by an anti-CD47 antibody is due to the presence of prophagocytic signals expressed mainly on tumor cells and not on normal cell counterparts {Chao 2010b}. In addition, the anti-CD47 antibody can induce an anticancer T-cell response through cross-presentation of tumor antigens by macrophage and antigen-presenting cells after tumor cell phagocytosis {Liu 2015b, Tseng 2013}.

Magrolimab is a humanized anti-CD47 mAb that blocks the interaction of CD47 with its receptor and enables phagocytosis of human cancer cells {Liu 2015a}. The activity of magrolimab is primarily dependent on blocking CD47 binding to SIRPα and not on the recruitment of crystallizable fragment (Fc)-dependent effector functions, although the presence of the immunoglobulin G 4 (IgG4) Fc domain is required for its full activity. For this reason, magrolimab was engineered with a human IgG4 isotype that is relatively inefficient at recruiting Fc-dependent effector functions that might enhance toxic effects on normal CD47-expressing cells {Liu 2015a}. Nonclinical studies using xenograft cancer models provide compelling evidence that magrolimab triggers phagocytosis and elimination of cancer cells from human solid tumors and hematologic malignancies. Based on this mechanism of action (MOA) and its potent nonclinical activity, magrolimab is being developed as a novel therapeutic candidate for solid tumors and hematologic malignancies.

The magrolimab clinical development program represents a novel strategy for the treatment of cancer and is the first therapeutic agent to target the CD47-SIRPα axis. Extensive nonclinical studies have demonstrated activity against both human solid tumors (breast, ovarian, pancreas, colon, leiomyosarcoma, bladder, prostate, and others) and hematologic malignancies (AML, acute lymphoblastic leukemia, non-Hodgkin lymphoma [NHL], myeloma, myelodysplastic syndrome [MDS], and others).

As described in Edition 8 of the magrolimab investigator's brochure (IB), magrolimab is being investigated as an anticancer therapeutic in 6 ongoing clinical studies in the United States (US) and United Kingdom, as monotherapy or in combination with other therapeutics, for the treatment of NHL, colorectal cancer (CRC), AML, MDS, and ovarian cancer. A total of 568 patients have been treated as of the data cut-off dates in the magrolimab IB, Edition 8.

While magrolimab has single-agent nonclinical and clinical activity, efficacy is best enhanced in combination with other anticancer agents. Nonclinical and clinical studies have shown that magrolimab combinations with cytotoxic agents can enhance prophagocytic signals on tumor cells through cytotoxicity, which can lead to synergistic phagocytosis of tumor cells and enhanced activity. Consequently, magrolimab is being evaluated clinically in several combinations with cytotoxic agents including chemotherapy.

For further information on magrolimab, refer to the current IB.

1.2.2. Nonclinical Pharmacology and Toxicology

1.2.2.1. Pharmacology

In vitro studies of magrolimab activity included protein and cell-based assays using cancer cell lines. Magrolimab showed high binding affinity to monomeric and bivalent human CD47 antigen, with a dissociation constant (K_D) of 8×10^{-9} and 8×10^{-12} M, respectively. Magrolimab bound to cynomolgus monkey and human CD47 with high affinity of $K_D = 10$ and 8.0 pM, respectively, but did not bind to mouse CD47. No complement-dependent cytotoxicity activity of magrolimab was observed in AML cells, and no antibody-dependent cell-mediated cytotoxicity activity of magrolimab was observed in Raji and HL60 cells. Magrolimab-induced macrophage-mediated phagocytosis in rat myeloma and HL60 cells and did not induce apoptosis in AML cells. Expression of CD47 was observed on human peripheral blood cells, and magrolimab did not trigger phagocytosis by human macrophages of normal red blood cells (RBCs) or normal human bone marrow cells in vitro but was a potent inducer of phagocytosis of CD47-expressing AML cells in vitro. Treatment of AML cells with hydroxyurea had no effect on magrolimab-induced phagocytosis, nor did hydroxyurea treatment trigger magrolimab-induced phagocytosis of normal bone marrow cells. In contrast, the combination of magrolimab and avelumab effectively enhanced phagocytosis of ovarian cancer cells by human macrophages compared to magrolimab or avelumab alone. Moreover, the combination of magrolimab with cytotoxic agent azacitidine at a clinically relevant concentration enhanced phagocytosis of HL60 cells in vitro when compared to magrolimab or azacitidine alone.

Nonclinical in vivo pharmacology studies using xenograft cancer models provide compelling evidence that magrolimab triggers phagocytosis and elimination of cancer cells from multiple human solid tumors and hematologic malignancies. Overall, magrolimab in combination with azacitidine, trastuzumab, rituximab, cetuximab, and panitumumab demonstrated an additive effect on eliminating cancer cells, resulting in a long-term remission and increased survival of animals.

Receptor occupancy (RO) assays showed that optimal antitumor activity (phagocytosis) in HL60 cells and primary human AML cells could be achieved without full CD47 RO.

The safety pharmacology evaluations as part of a Good Laboratory Practice 8-week toxicology study demonstrated no magrolimab-related effects on central nervous system (CNS), cardiovascular, or respiratory function in cynomolgus monkeys.

1.2.2.2. Toxicology

In in vitro studies, magrolimab was not hemolytic and there was no evidence of adverse elevations of proinflammatory cytokines.

In the pivotal 8-week repeat-dose toxicology study, magrolimab was administered to cynomolgus monkeys via a 1-hour intravenous (IV) infusion as a priming dose of 5 mg/kg in Week 1 (Day 1), followed by twice-weekly maintenance doses for 7 consecutive weeks at doses ranging from 5 to 100 mg/kg. Treatment-related findings were limited to changes in hematology

and clinical chemistry parameters and erythroid cell morphology. Hematology changes included decreases in RBC mass associated with decreases in mean corpuscular volume and haptoglobin; increases in mean corpuscular hemoglobin concentration, reticulocytes, and RBC distribution width; RBC morphology changes including spherocytes (microcytes), eccentrocytes, atypical erythrocyte fragments consistent with erythrocyte injury, erythrocyte clumping, and large platelets; and changes associated with increased erythropoiesis consisting of anisocytosis, polychromatophilic macrocytes, and increased total bilirubin. Changes in blood cell morphology were consistent with previous studies and considered to be associated with accelerated RBC destruction/clearance and increased erythropoiesis.

Additional clinical chemistry changes were observed at the highest dose only (100 mg/kg), which included a slight decrease in albumin, a slight increase in globulin, and a corresponding decrease in albumin:globulin ratio. There was partial to complete recovery for all treatment-related changes except for increased spleen weights in males and females at 50 and 100 mg/kg at recovery necropsy, which had no macroscopic or microscopic correlate. Based on these results, the highest nonseverely toxic dose for this study was considered to be 100 mg/kg, the highest dose evaluated.

Reproductive and developmental toxicology studies have not been conducted, but all the available data (literature, data from knockout mice, and limited clinical data) suggest no role for CD47 in embryo-fetal development. Moreover, notably, a waiver has been granted by the US Food and Drug Administration (FDA) for conducting embryo-fetal studies for magrolimab, as in most cases magrolimab is utilized in combination with other products that most likely have contraindications in women of childbearing age.

1.2.3. Clinical Background for Magrolimab

1.2.3.1. Summary of Clinical Pharmacology

Clinical pharmacokinetic (PK) data have been collected in all ongoing studies of magrolimab conducted to date. Pharmacokinetic data have been analyzed in a Phase 1 study (SCI-CD47-001) in patients with solid tumors and lymphomas. In this study, patients were treated with weekly magrolimab doses ranging from 0.1 to 45 mg/kg, with increasing serum concentrations associated with increasing dose. Nonlinear PK consistent with target-mediated clearance was observed over this dose range. However, at maintenance doses of 10 mg/kg and above, target-mediated clearance was saturated within the dosing regimen, and trough levels associated with magrolimab efficacy in nonclinical studies were achieved. Nine of 88 (10%) evaluable patients tested positive for antidrug antibody (ADA) against magrolimab at any time point including baseline; ADA positivity had no impact on PK or clinical safety in these patients.

In a Phase 1 AML study (SCI-CD47-002), as in the solid tumor Phase 1 study, nonlinear PK consistent with target-mediated clearance was observed. Three of 20 (15%) evaluable patients tested positive for ADA against magrolimab at any time point including baseline; ADA positivity had no impact on PK. Antidrug antibody positivity in either study was not associated with increased adverse events (AEs).

Preliminary PK data from other ongoing studies (5F9003, 5F9004, and 5F9005) of magrolimab indicate similar PK properties across all tumor populations and in the presence of coadministered drugs. Across all studies, 46 of 430 (11%) patients tested positive for ADA against magrolimab at any time point including baseline. Antidrug antibody positivity was not associated with changes in PK or AE profile.

A preliminary population PK analysis of combined magrolimab PK data indicated that results for magrolimab population PK were typical of other nonlinear antibodies. No clinically significant covariates of PK variability were identified.

1.2.3.2. Summary of Clinical Safety

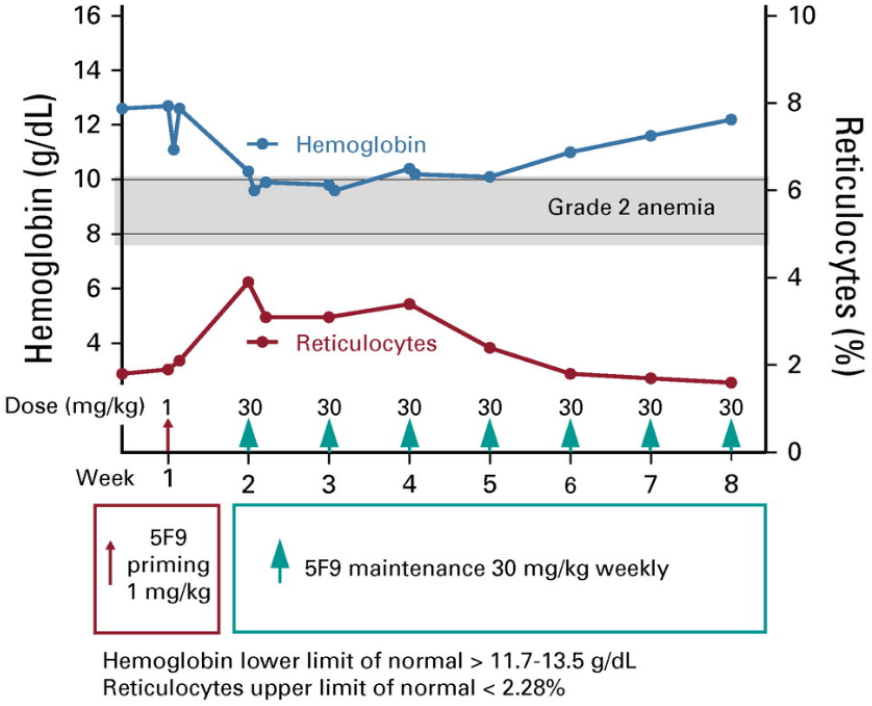
Magrolimab is administered as an IV infusion and it is currently being studied in 6 clinical studies, as noted above. Two completed single-agent Phase 1 studies include Study SCI-CD47-001 in patients with advanced solid tumors and lymphomas, and Study SCI-CD47-002 in patients with relapsed/refractory (r/r) AML, along with 2 Phase 1b partnered studies in AML as well as urothelial cancer. Four combination studies include the following: Study 5F9003, a Phase 1b/2 study of magrolimab with rituximab in patients with r/r NHL; Study 5F9004, a Phase 1b/2 study of magrolimab with cetuximab in patients with solid tumors and CRC; Study 5F9005, a Phase 1b study of magrolimab with azacitidine in patients with AML and MDS; and Study 5F9006, a Phase 1b study of magrolimab with avelumab in patients with solid tumors and ovarian cancer. As of July 2020, over 500 patients have been treated with magrolimab. Overall, the safety profile has been acceptable with magrolimab as monotherapy or in combination, with no maximum tolerated dose (MTD) reached in any study with dosing up to 45 mg/kg. Two anticipated adverse reactions included on-target anemia and infusion-related reactions (IRRs), which are expected with mAbs. Importantly, on-target anemia due to CD47 blockade-mediated RBC clearance was mitigated with a priming/maintenance dose strategy. The average hemoglobin decline with the first (priming) dose was between approximately 0.4 to 1.5 g/dL across indications, with many patients' hemoglobin improving on therapy back to baseline, with a decrease in RBC transfusion requirements for those patients who were transfusion-dependent at baseline.

Magrolimab has been evaluated as a monotherapy or in combination in multiple solid tumor types. In the Phase 1 Study SCI-CD47-001 of magrolimab monotherapy, 88 patients with advanced solid tumors were treated with magrolimab doses up to 45 mg/kg. No MTD was reached. As described in the 2020 IB, across 548 patients treated with magrolimab, which includes both solid tumors and hematologic malignancies, fatigue, anemia, and headache were the 3 most frequently reported AEs (43.0%, 40.8%, and 36.4% of patients, respectively). Patients experienced mostly Grade 1 and 2 fatigue (2.8% of patients reported severe fatigue).

Anemia is the most common treatment-related AE, reported in 35.4% of patients. Approximately 13% of all patients experienced anemia Grade 1 or 2, and 22% severe anemia. Notably, many of those patients with severe anemia were patients with AML and MDS, who have severe anemia at baseline. Anemia was typically manifested as a decline in hemoglobin observed within the first 2 weeks of treatment. The initial decrease in hemoglobin after the first dose is on average 0.5 to 2 g/dL. In patients with solid tumors, the fall in hemoglobin was followed by a compensatory

reticulocytosis, with many patients experiencing a gradual return to baseline despite continued dosing. The changes in hemoglobin and reticulocytes described with magrolimab treatment are fairly consistent across tumor types and are shown in Figure 1. Hyperbilirubinemia (predominately unconjugated) indicates extravascular hemolysis consistent with phagocytic removal of RBCs arising from the blockade of CD47 signaling. Administration of a low priming dose of magrolimab mitigated on-target anemia, an effect that is mostly observed after the first dose.

Figure 1. Effect of Magrolimab on Anemia and Mitigation With a Priming/Maintenance Dosing Regimen



5F9 = magrolimab
The red blood cell profile of a solid tumor patient treated with magrolimab monotherapy is shown {Sikic 2019}.

Infusion-related reactions are also a commonly observed AE with magrolimab. In total, 29% of patients reported at least 1 IRR. Most common signs/symptoms of IRRs related to magrolimab included chills, pyrexia, back pain, headache, nausea, vomiting, dyspnea, anemia, and blood bilirubin increase. These IRRs were generally observed during the initial 2 doses of magrolimab. Current recommendations for premedication and IRR management are described in Sections 5.8 and 7.8.1.3. Lastly, hemagglutination (RBC agglutination) as observed on the peripheral smear is a common treatment effect and was reported as a treatment-related AE in 11.8% of all patients.

Transient hemagglutination is observed after the initial priming or first maintenance dose of drug; however, it is less common thereafter, and it has not been consistently correlated with any clinical sequelae.

In summary, as of July 2020, 568 patients (346 solid tumor/lymphoma patients and 222 AML/MDS patients) have been treated with magrolimab as monotherapy or in combination. Based on this aggregate safety data, magrolimab has an acceptable safety profile both as monotherapy and in combination with other agents (rituximab, gemcitabine, oxaliplatin, cetuximab, avelumab, or azacitidine) across multiple advanced solid tumor and hematologic malignancies. Refer to the magrolimab IB for further details.

1.2.3.3. Summary of Clinical Efficacy

Clinical efficacy with magrolimab has been observed in multiple hematologic and solid tumor malignancies. In the Phase 1 Study SCI-CD47-001 of magrolimab monotherapy in advanced solid tumors, 2 patients with clear cell ovarian and fallopian tube carcinomas achieved a partial response per Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.1), with time to progression of 5.2 and 9.2 months, respectively {Sikic 2019}. In the Phase 1b/2 study of magrolimab in combination with cetuximab in r/r CRC patients (Study 5F9004), 2 objective responses among 32 patients (6%) were observed in r/r metastatic KRAS wildtype CRC patients who were refractory to cetuximab, with a disease control rate of 50% {Fisher 2020}. The OS in KRAS wildtype and KRAS mutant CRC patients treated with magrolimab and cetuximab was 9.5 and 7.6 months, respectively. These data may compare favorably to historical data in KRAS wildtype and mutant patients treated with standard of care, with a median OS of 8.0 and 6.5 months, respectively {Van Cutsem 2018}.

In hematologic malignancies, efficacy has been observed in NHL, MDS, and AML. In study 5F9003, patients with r/r NHL were treated with magrolimab in combination with rituximab. In 97 NHL patients evaluable for efficacy (malignancies included diffuse large B-cell lymphoma [DLBCL] and indolent lymphoma), the objective response rate (ORR) was 45%, with a complete response rate of 19%. The ORR in DLBCL was 36% in 59 patients and 61% for 38 indolent lymphoma patients treated. In Study 5F9005, patients with untreated AML ineligible for induction chemotherapy and untreated, higher-risk MDS patients were treated with magrolimab in combination with azacitidine. In 25 AML patients, the ORR was 64% and CR rate was 40%. In 33 MDS patients, the ORR was 91% and CR rate was 42%. No median duration of response (DOR) was reached for either cohort, with median follow-up period of 9.4 months for AML and 5.8 months for MDS.

In summary, magrolimab has demonstrated combination efficacy across both solid tumors and hematologic malignancies. Refer to the magrolimab IB for further details.

1.3. Information About Nab-paclitaxel, Paclitaxel, and Sacituzumab Govitecan

1.3.1. Description of Nab-paclitaxel

Nab-paclitaxel (Abraxane) is a nanoparticle albumin-bound microtubule inhibitor and taxane indicated for the treatment of metastatic breast cancer after failure of combination chemotherapy for metastatic disease. Nab-paclitaxel is also approved in some countries in combination with atezolizumab for adult patients with mTNBC whose tumors express PD-L1 {Abraxane® 2005 }.

1.3.1.1. Clinical Data for Nab-paclitaxel

Nab-paclitaxel is indicated for multiple cancer types, including metastatic breast cancer and mTNBC (for patients whose tumors express PD-L1), in combination with atezolizumab {Abraxane® 2005 }.

The most common AEs (at least 20%) in patients with metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal electrocardiogram (ECG), fatigue/asthenia, myalgia/arthralgia, aspartate aminotransferase (AST) elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea {Abraxane® 2008, Abraxane® 2005 }. Nab-paclitaxel is contraindicated in patients who have neutrophil counts less than 1500 cells/mm^3 and carries a black box warning. Nab-paclitaxel is also contraindicated in patients with severe hypersensitivity reaction to the drug. Nab-paclitaxel causes myelosuppression, sensory neuropathy, severe hypersensitivity reactions, and potential fetal harm.

Nab-paclitaxel is approved as monotherapy in metastatic breast cancer and in combination with atezolizumab in mTNBC for patients whose tumors express PD-L1. As a monotherapy, nab-paclitaxel was compared to paclitaxel in a randomized Phase 3 study in metastatic breast cancer patients who had failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy. Nab-paclitaxel had a statistically significantly higher ORR of 21.5% compared to 11.1% for control {Abraxane® 2008, Abraxane® 2005 }. There was no statistically significant difference in OS between the 2 study arms.

The approval for 1L, PD-L1–positive TNBC was based on a randomized Phase 3 study evaluating atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel {Schmid 2018}. In 451 patients, the median PFS was 7.2 months with atezolizumab + nab-paclitaxel, as compared with 5.5 months with placebo + nab-paclitaxel ($P = 0.002$). Among patients with PD-L1–positive tumors, the median PFS was 7.5 months and 5.0 months for experimental and control arms, respectively (HR: 0.62; $P < 0.001$). These data formed the basis for the approval of nab-paclitaxel + atezolizumab in PD-L1-positive mTNBC in the European Union (EU) in August 2019.

1.3.2. Description of Paclitaxel

Paclitaxel, sold under the brand name Taxol® among others, is a natural product (obtained via a semisynthetic process from the Pacific yew tree [*Taxus brevifolia*]) with antitumor activity. It promotes the assembly and stabilization of microtubules, while inhibiting their depolymerization, and thus results in inhibition of mitosis and cell death. Common side effects include nausea and vomiting, loss of appetite, neutropenia, alopecia, anemia, arthralgia/myalgia, diarrhea, leukopenia, opportunistic infections, peripheral neuropathy, thrombocytopenia, mucositis, hypersensitivity, renal impairment, and hypotension. Dexamethasone is usually administered prior to paclitaxel infusion to mitigate some of the side effects.

1.3.2.1. Clinical Data for Paclitaxel

In the US, paclitaxel is approved for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy; it is also approved as single-agent for the treatment of metastatic breast cancer (mBC) after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Approval was based on a Phase 3 study of 2 different doses (175 mg/m^2 versus 135 mg/m^2) of Cremophor EL-dissolved paclitaxel given every 3 weeks in patients with mBC whose disease had progressed on or after previous chemotherapy {Nabholtz 1996}. Compared to the lower dose, the higher dose was associated with a longer median time to disease progression (4.2 versus 3.0 months, respectively; $P = 0.027$) and a longer median OS (11.7 versus 10.5 months, respectively; $P = 0.321$). In the EU, paclitaxel is approved as monotherapy for late mBC and in combination with bevacizumab as 1L treatment.

The combination of pembrolizumab with a choice of chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine/carboplatin) received approval by the FDA based on the results of the KEYNOTE 355 study for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS at least 10) as determined by an FDA-approved test.

1.3.3. Description of Sacituzumab Govitecan

Sacituzumab govitecan sold under the brand name Trodelvy® is an antibody-drug conjugate composed of 3 compounds: a humanized monoclonal antibody, a topoisomerase I inhibitor, and linker protein. It binds to Trop-2 expressing cells, forming an internalized complex that releases SN-38 intracellularly. SN-38 binds to topoisomerase I-DNA complexes, causing DNA damage and apoptosis. Common side effects include nausea, vomiting, diarrhea, neutropenia, anemia, fatigue, alopecia, constipation, decreased appetite, leukopenia, hyperglycemia, and hypomagnesemia {Bardia 2017}.

1.3.3.1. Clinical Data for Sacituzumab Govitecan

Sacituzumab govitecan is approved in several countries, including the US, Canada, EU, and Australia, for the treatment of unresectable locally advanced or mTNBC. Approval for TNBC was based on the ASCENT protocol, a Phase 3, multicenter study with 468 patients with relapsed/refractory TNBC {Bardia 2021}. Patients were randomly assigned to receive sacituzumab govitecan (235 patients) or chemotherapy (233 patients). The median age was 54 years, all patients were previously treated with taxanes and had no brain metastases. Sacituzumab govitecan was dosed at 10 mg/kg on Days 1 and 8 every 21 days until progression or unacceptable toxicity. Sacituzumab govitecan demonstrated a longer median PFS (5.6 vs 1.7 months), and longer median OS (12.1 vs 6.7 months) than the chemotherapy arm. The percentage of patients with an objective response was 35% with sacituzumab govitecan and 5% with chemotherapy. The incidences of key treatment-related AEs of Grade 3 or higher were neutropenia (51% with sacituzumab govitecan and 33% with chemotherapy), leukopenia (10% and 5%), diarrhea (10% and < 1%), anemia (8% and 5%), and febrile neutropenia (6% and 2%). There were 3 deaths owing to AEs in each group; no deaths were considered to be related to sacituzumab govitecan treatment.

1.4. Rationale for Cohort 1

Strong nonclinical and clinical rationale exists for combining magrolimab with chemotherapy agents, including taxanes. Chemotherapeutic agents have been demonstrated to enhance prophagocytic signals on tumor cells, which leads to synergistic antitumor activity when combined with magrolimab, a CD47-targeting antibody that blocks the antiphagocytic signal. Simultaneous blockade of the antiphagocytic signal CD47 by magrolimab with upregulation of prophagocytic signals via chemotherapies can lead to synergistic phagocytosis of tumor cells by macrophages. Indeed, magrolimab combination with taxanes (paclitaxel) led to enhanced phagocytosis of solid tumor cells in vitro and a statistically significant reduction and elimination of ovarian cancers in vivo when compared to single-agent therapy {Sikic 2016}. Clinically, magrolimab has been combined with cytotoxic agents and chemotherapy (including azacitidine, gemcitabine, and oxaliplatin) in hematologic malignancies including AML, MDS, and NHL. These agents also upregulate prophagocytic signals and have led to enhanced combination activity with magrolimab in nonclinical models. In the clinical setting, magrolimab and azacitidine have led to a 91% ORR in patients with untreated higher-risk MDS and a 64% ORR in untreated AML patients {Sallman 2020}. Combination efficacy also has been observed with magrolimab in combination with chemotherapeutic agents (gemcitabine, oxaliplatin, and rituximab) in patients with r/r DLBCL. Importantly, the addition of magrolimab to these cytotoxic/chemotherapeutic agents did not generally exacerbate toxicities and the combination had an acceptable safety profile, with no MTD reached (Section 1.2.3.3).

Patients with newly diagnosed mTNBC are generally treated with either taxane-based chemotherapy or an immune checkpoint inhibitor (atezolizumab) in combination with taxane for those patients whose tumors express PD-L1. While the recent approval of atezolizumab + nab-paclitaxel has improved PFS in the frontline mTNBC setting, this effect was most pronounced in those patients whose tumors were PD-L1 positive. These results led to the approval of atezolizumab in combination with nab-paclitaxel in PD-L1–positive mTNBC patients. Additional immune checkpoint inhibitors combined with taxane therapy are also being evaluated in the frontline mTNBC setting. Despite these advances, single-agent taxane therapy remains a standard for newly diagnosed mTNBC patients whose tumors are PD-L1 negative. PD-L1–negative mTNBC is seen in approximately 35% to 60% of patients {Marra 2019}. Outcomes with single-agent taxane therapy in mTNBC remain suboptimal, with response rates approximately 30%, PFS around 5 months, and OS around 12 to 18 months {Kim 2017, Schmid 2018, Tutt 2018}. Thus, novel regimens that can safely and effectively be combined with taxanes are needed to improve the clinical benefit in PD-L1–negative frontline mTNBC patients. Strong nonclinical and clinical data support the evaluation of magrolimab in combination with chemotherapy, including taxanes, in patients with newly diagnosed mTNBC.

The objective of this Phase 2 study cohort is to evaluate the safety, tolerability, and recommended Phase 2 dose (RP2D) of magrolimab in combination with nab-paclitaxel or paclitaxel in patients previously untreated for unresectable, locally advanced or metastatic TNBC whose tumors are not appropriate for immune checkpoint inhibitor therapy. In the randomized portion, the efficacy and safety of magrolimab in combination with the choice of nab-paclitaxel or paclitaxel will be compared against nab-paclitaxel or paclitaxel in the same patient population.

In this study, 2 combination regimens will be investigated, namely magrolimab + nab-paclitaxel and magrolimab + paclitaxel. Nab-paclitaxel or paclitaxel have been selected as the combination partners for magrolimab and comparator given their lack of significant overlapping toxicities with magrolimab and their common use in mTNBC, including recent data in combination with pembrolizumab and atezolizumab. This approach allows for the inclusion of the most commonly used single-agent chemotherapy class (taxanes). The rationale for allowing for the choice of either nab-paclitaxel and paclitaxel accounts for variability in availability of the 2 agents across the globe, clinical use worldwide, as well as generally comparable benefit observed in terms of PFS in the recent 1L TNBC studies (KEYNOTE 355 and IMpassion130).

In summary, a strong nonclinical and clinical rationale exists for evaluating a combination of magrolimab and nab-paclitaxel or paclitaxel in untreated mTNBC patients.

1.4.1. Rationale for Cohort 2

Overexpression of CD47 has been reported in TNBC and is a poor prognostic factor for disease-free survival {Yuan 2019}. Additionally, there are data to suggest that CD47 is upregulated in chemotherapy-treated TNBC cells indicating that CD47 is an ideal target to treat drug-resistant or chemotherapy-treated TNBCs {Si 2021}. Although sacituzumab govitecan has demonstrated a significant increase in PFS in heavily pretreated patients with TNBC when compared to standard-of-care therapy, there is still room for additional improvement for patients who fail initial treatment for advanced TNBC. Sacituzumab govitecan was developed to treat cancers by binding to Trop-2 for targeted delivery of SN-38 directly to the tumor cell while minimizing systemic exposure of SN-38 to decrease host toxicity. The Trop-2 antigen is highly expressed on most solid epithelial cancers, including TNBC. Sacituzumab govitecan causes DNA damage and apoptosis, which can serve as the second pro-apoptotic signal needed in tumor cells exposed to magrolimab. We believe that the addition of magrolimab to sacituzumab govitecan will have an added antitumor effect due to the expression of CD47 and Trop-2 on TNBC tumor cells without a significant increase in toxicity due to nonoverlapping safety profiles (Section 1.6).

1.5. Rationale for Dose Selection of Magrolimab

The rationale for the magrolimab dose proposed in this study originates from safety, efficacy, and PK/pharmacodynamics (PD) data and modeling and simulation analyses based on data obtained from all ongoing and completed clinical studies with magrolimab in patients with solid tumors, NHL, and AML/MDS.

In the first-in-human study of magrolimab (SCI-CD47-001) in patients with solid tumors and lymphomas, after an initial priming dose of 1 mg/kg on the first day, magrolimab was tested as a monotherapy at weekly doses of up to 45 mg/kg. The use of an initial 1 mg/kg priming dose was integrated into the dosing regimen to mitigate the on-target anemia induced by CD47 blockade. An initial priming dose leads to elimination of aged RBCs that are sensitive to CD47 blockade and triggers reticulocytosis of young RBCs that are not affected by CD47 blockade{Chen 2018}. Utilizing a priming dose leads to an initial, transient, and mild anemia that generally normalizes back to baseline over several weeks, even in the presence of repeated therapeutic doses of

magrolimab {Advani 2018, Liu 2015a, Sikic 2019}. Based on PK-PD modeling, a maintenance dose of 30 mg/kg every 2 weeks is expected to provide more than 90% occupancy of the CD47 receptor in peripheral blood and tumor tissues and thus is expected to provide maximal efficacy while maintaining adequate safety. In solid tumors where the combination therapy is given according to 3-week cycles, dosing of magrolimab every 3 weeks optimizes patient and caregiver convenience. Magrolimab 60 mg/kg every 3 weeks is predicted to provide a similar trough concentration and RO as the 30 mg/kg every 2 weeks dose, the dose being used in Phase 3 studies in AML and MDS. Updated PK modeling from Study 5F9005 showed that the magrolimab dose of 45 mg/kg every 3 weeks was suboptimal compared to 30 mg/kg every 2 weeks and 60 mg/kg every 3 weeks dosing in maintaining trough concentration. Maintaining adequate trough concentration may be necessary for optimal efficacy considering that some patients may experience dose delays due to toxicity. Furthermore, the PK-PD modeling also indicates that at these extended interval dosing regimens, the RO will be maintained at maximal levels (> 90%) in peripheral blood and tumor tissues. The proposed dosing regimen of magrolimab in this study is expected to have an acceptable safety profile based on the entirety of safety data in multiple oncology populations, both as a monotherapy and in combination with other tumor-targeted antibodies and chemotherapeutics.

1.5.1. Safety Run-in Cohorts 1 and 2 and Phase 2 Cohorts 1 and 2

The following magrolimab dosing regimen is proposed for Safety Run-in Cohort 1 and Phase 2 Cohort 1 over a 28-day cycle:

- Cycle 1: priming (1 mg/kg) on Day 1 and 30 mg/kg on Days 8, 15, and 22
- Cycle 2: weekly doses of 30 mg/kg on Days 1, 8, 15, and 22
- Cycle 3 and onward: 30 mg/kg on Days 1 and 15

The following magrolimab dosing regimen is proposed for Safety Run-in Cohort 2 and Phase 2 Cohort 2 over a 21-day cycle:

- Cycle 1: priming (1 mg/kg) on Day 1 and 30 mg/kg on Days 8 and 15
- Cycle 2: weekly doses of 30 mg/kg on Days 1, 8, and 15
- Cycle 3 and onward: 60 mg/kg on Day 1

1.6. Risk/Benefit Assessment for the Study

Patients with metastatic solid tumors who fail frontline combination chemotherapy and/or immune checkpoint inhibitor therapy have limited treatment options with a poor prognosis. In general, single-agent chemotherapy (ie, taxanes) are utilized in this setting across several solid tumor types. However, response rates are approximately 10%, with a limited median OS. Thus, novel therapies that can be safely combined with chemotherapy to enhance efficacy are needed in this high-unmet-need patient setting. Patients with newly diagnosed mTNBC whose tumors

are PD-L1–negative are treated with single-agent taxane therapy. However, prognosis is limited, with a median PFS of approximately 5 months. As in the relapsed solid tumor setting, novel agents that can be combined safely with taxanes to enhance efficacy are needed to improve patient outcomes in PD-L1–negative mTNBC.

Magrolimab can eliminate tumor cells through macrophage-mediated phagocytosis. Magrolimab activity can be enhanced with chemotherapeutic agents that can increase prophagocytic signals on tumor cells, leading to synergistic phagocytosis. Nonclinical data have shown that magrolimab in combination with taxanes leads to enhanced phagocytosis of solid tumor cells in vitro and prolonged remissions in xenograft models compared to single-agent therapy. Furthermore, clinical study data has shown that magrolimab can enhance the efficacy of cytotoxic agents including an over 90% ORR in patients with newly diagnosed, higher-risk MDS with magrolimab in combination with azacitidine {Sallman 2020}. A combination study with magrolimab and traditional chemotherapy (gemcitabine, oxaliplatin, and rituximab) is ongoing in patients with NHL that has also shown initial signs of activity and an acceptable safety profile. Thus, the scientific rationale, nonclinical, and clinical data support a combination of magrolimab with taxane chemotherapy, including nab-paclitaxel or paclitaxel.

Treatment with the proposed combination of magrolimab and nab-paclitaxel or paclitaxel for mTNBC is not anticipated to pose a significantly increased risk to patients enrolled in this study compared to the risk of treatment with the agents alone. Based on the clinical profiles of magrolimab, nab-paclitaxel, and paclitaxel, overlapping toxicities (except for potential anemia and neutropenia) are not anticipated with the combination. While magrolimab does cause a transient, generally mild to moderate anemia, nab-paclitaxel, paclitaxel, and sacituzumab govitecan generally induces Grade 1 or 2 anemia in patients. Potential anemia observed is managed by a priming/maintenance dose regimen for magrolimab, frequent laboratory monitoring of blood counts, and RBC transfusion guidance. Importantly, magrolimab does not cause overlapping toxicities that are significant to nab-paclitaxel or paclitaxel, including hepatotoxicity or neurological toxicities. Specific clinical and laboratory monitoring of magrolimab-, nab-paclitaxel-, and paclitaxel-related toxicities will be implemented in this study. Furthermore, magrolimab has been combined with cytotoxic chemotherapy (gemcitabine, oxaliplatin, and rituximab in NHL patients) without observation of exacerbation of chemotherapy toxicities, with an acceptable safety profile, and with no MTD reached. Thus, the anticipated safety profile of magrolimab with taxane combinations represent an acceptable risk-benefit ratio to patients.

Magrolimab when given in combination with other chemotherapeutic agents in patients with solid tumors and hematologic malignancies has shown promising activity. Sacituzumab govitecan has been approved in several countries for the treatment of advanced TNBC based on the significant improvement in PFS and OS as compared to standard-of-care therapy. As demonstrated by other chemotherapeutic agents, sacituzumab govitecan may enhance the prophagocytic signals on tumor cells producing synergistic activity when combined with magrolimab. The addition of magrolimab can potentially improve the established activity of sacituzumab govitecan in patients with unresectable locally advanced or mTNBC.

The safety profile of magrolimab in combination with sacituzumab govitecan is also expected to be acceptable. As described in Section 1.3.3.1, key Grade 3 or higher treatment-related AEs for sacituzumab govitecan were neutropenia, leukopenia, diarrhea, anemia, and febrile neutropenia. Based on the clinical profiles of magrolimab and sacituzumab govitecan, significant overlapping toxicities (except for anemia and potentially diarrhea) are not anticipated with the combination. While magrolimab has been associated with diarrhea, the vast majority of these events have been Grade 1 or 2 in severity. Therefore, the anticipated safety profile of magrolimab in combination with sacituzumab govitecan represents an acceptable risk-benefit ratio to patients.

During a pandemic, additional potential risks to patients 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 3 for further details on the risks and risk mitigation strategy.

In summary, based on a strong scientific rationale, nonclinical and emerging clinical data, limited overlapping toxicities, and the risk mitigation measures being implemented for the pandemic, the evaluation of magrolimab in combination with nab-paclitaxel or paclitaxel or sacituzumab govitecan in patients with mTNBC is anticipated to have an acceptable risk-benefit ratio to the patients enrolled in this study.

1.7. Compliance

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

2. OBJECTIVES AND ENDPOINTS

Table 1 presents the study objectives and endpoints. The analysis of the endpoints is described in Section 8.

Table 1. Study Objectives and Endpoints

Primary Objectives	Primary Endpoints
Safety Run-in Cohort 1: • To evaluate the safety, tolerability, and RP2D of magrolimab in combination with nab-paclitaxel or paclitaxel Phase 2 Cohort 1: • To compare the efficacy of magrolimab in combination with nab-paclitaxel or paclitaxel versus nab-paclitaxel or paclitaxel alone as determined by progression-free survival (PFS) by investigator assessment Safety Run-in Cohort 2: • To evaluate the safety, tolerability, and RP2D of magrolimab in combination with sacituzumab govitecan Cohort 2 (Safety Run-in Cohort 2 and Phase 2 Cohort 2): • To evaluate the efficacy of magrolimab in combination with sacituzumab govitecan as determined by confirmed ORR by investigator assessment	Safety Run-in Cohorts 1 and 2: • Incidence of dose-limiting toxicities (DLTs), AEs, and laboratory abnormalities according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 Phase 2 Cohort 1: • PFS, defined as the time from the date of randomization until the earliest date of documented disease progression as determined by investigator assessment using RECIST, Version 1.1, or death from any cause, whichever occurs first Cohort 2 (Safety Run-in Cohort 2 and Phase 2 Cohort 2): • Confirmed ORR (defined as the proportion of patients who achieve complete response or partial response that is confirmed at least 4 weeks after initial documentation of response), as determined by investigator assessment per RECIST, Version 1.1
Secondary Objectives	**Secondary Endpoints**
Phase 2 Cohort 1: • To compare the efficacy between treatment arms by ORR by investigator assessment • To compare the efficacy between treatment arms by additional measures of efficacy, including DOR and OS • To compare the safety and tolerability between treatment arms Cohort 2 (Safety Run-in Cohort 2 and Phase 2 Cohort 2): • To evaluate PFS by investigator assessment • To evaluate additional measures of efficacy of magrolimab in combination with sacituzumab govitecan, including DOR and OS • Safety and tolerability of magrolimab in combination with sacituzumab govitecan	Phase 2 Cohort 1 and Cohort 2 (Safety Run-in Cohort 2 and Phase 2 Cohort 2): • Confirmed ORR, as determined by investigator assessment per RECIST, Version 1.1 (only for Phase 2 Cohort 1) • PFS, as determined by investigator assessment per RECIST, Version 1.1, or death from any cause, whichever occurs first (only for Cohort 2) • DOR, defined as time from first documentation of complete response or partial response to the earliest date of documented disease progression as determined by investigator assessment, per RECIST, Version 1.1, or death from any cause, whichever occurs first • OS, defined as time from date of randomization to death from any cause • Incidence of AEs and laboratory abnormalities according to NCI CTCAE, Version 5.0

Safety Run-in Cohorts 1 and 2 and Phase 2 Cohorts 1 and 2: • To evaluate the pharmacokinetics (PK) and immunogenicity of magrolimab in combination with anticancer chemotherapies	Safety Run-in Cohorts 1 and 2 and Phase 2 Cohorts 1 and 2: • Magrolimab concentration versus time and ADA to magrolimab

[redacted]

3. STUDY DESIGN

3.1. Study Design

This is a Phase 2, randomized (Phase 2 Cohort 1 only), open-label, multicenter study to evaluate magrolimab in combination with either nab-paclitaxel or paclitaxel for patients with untreated, unresectable, locally advanced or mTNBC and magrolimab in combination with sacituzumab govitecan for patients with unresectable, locally advanced or metastatic TNBC who have received at least 1 and no more than 2 prior lines of treatment in the unresectable, locally advanced or metastatic setting. This study will consist of 2 Safety Run-in Cohorts:

- Safety Run-in Cohort 1: magrolimab in combination with the choice of nab-paclitaxel or paclitaxel administered in patients previously untreated for unresectable, locally advanced or mTNBC whose tumors are not appropriate for immune checkpoint inhibitor therapy.

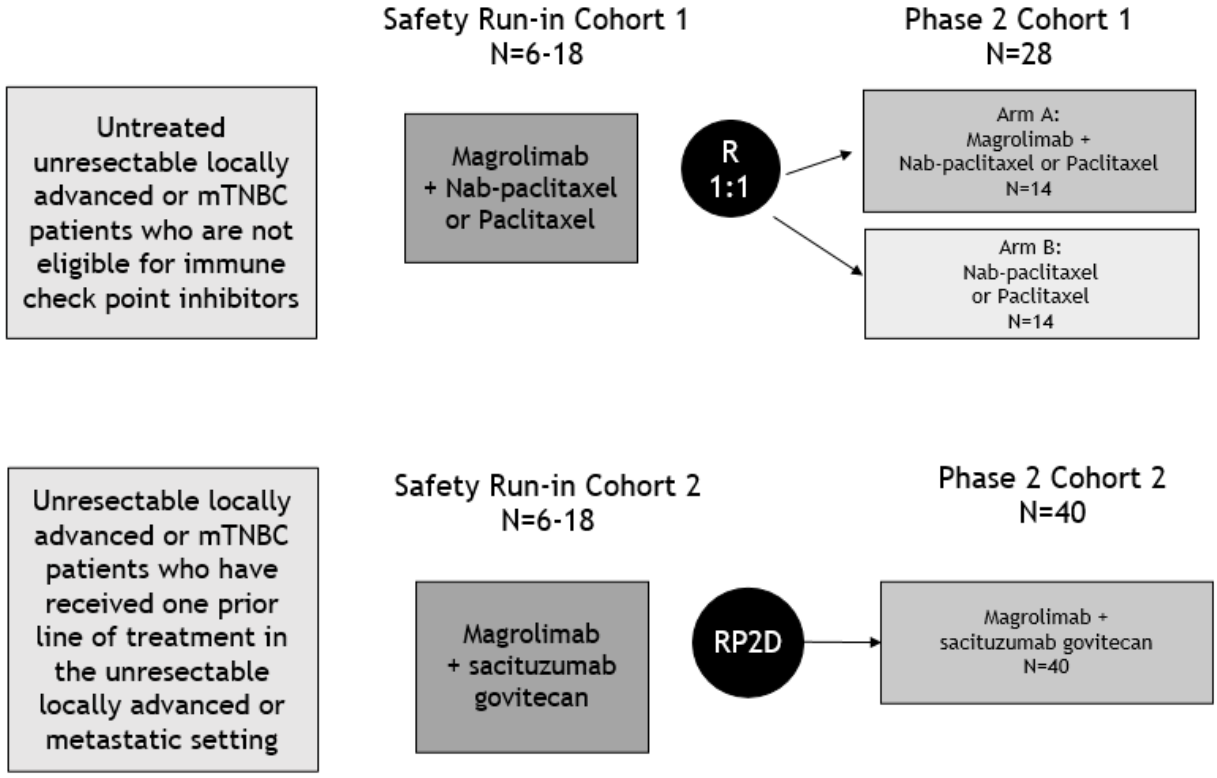
- Safety Run-in Cohort 2: magrolimab in combination with sacituzumab govitecan in patients with unresectable, locally advanced or mTNBC who have received at least 1 and no more than 2 prior lines of treatment in the unresectable, locally advanced or metastatic setting.

Once the safety review team (SRT) reviews each Safety Run-in Cohort and the sponsor determines the RP2D for that cohort, Phase 2 cohorts will be conducted as described in Section 3.1.2.

Patient participation will include screening, randomization (Phase 2 Cohort 1 only), treatment, and follow-up. Screening will last up to 30 days before the first dose of study treatment, during which time the patient's eligibility and baseline characteristics will be determined. Assessments performed as part of standard of care prior to informed consent form (ICF) signature may be used if they are within the required screening period. Patients will receive study treatment according to the dose schedule in Appendix Table 1 and Appendix Table 2.

The study schematic is presented in Figure 2.

Figure 2. Study Schema



mTNBC = metastatic triple-negative breast cancer; N = number of patients; R = ratio; RP2D = recommended Phase 2 dose

3.1.1. Safety Run-in Cohorts

Initially, up to 6 patients will be enrolled in Safety Run-in Cohort 1 at a starting dose level. A DLT evaluation period of 1 cycle (28 days) will occur.

Safety Run-in Cohort 2 will enroll up to 6 patients at a starting dose level. A DLT evaluation period of 1 cycle (21 days) will occur.

Even though no dose-dependent toxicities have been observed with magrolimab, in order to preserve the efficacious doses of the combination partner drugs, dose de-escalation will take place for magrolimab.

Cohorts 1 and 2 dose de-escalation decisions will be made as follows:

- If 2 or less of 6 DLT-evaluable patients experience a DLT in Cycle 1, enrollment into Phase 2 Cohort 1 or Phase 2 Cohort 2 may begin at this dose level as the RP2D.
- If more than 2 patients experience at least one DLT during Cycle 1, enrollment at the current dose level will immediately stop and dose de-escalation will occur. Approximately another 6 patients will then be enrolled and evaluated at a lower dose level in the same manner.

Approximately 18 patients (each cohort) could be potentially enrolled and evaluated during the Safety Run-in Cohorts.

Dose de-escalation for the Safety Run-in Cohorts is presented in Table 4 and Table 6. Based on the totality of the data, alternative doses of magrolimab not described in Table 4 or Table 6 may be considered by the SRT and sponsor.

3.1.1.1. DLT Assessment Period

DLT Assessment Period for Safety Run-in Cohort 1: The DLT assessment period will be the first cycle (28 days). Patients are considered evaluable for assessment of a DLT if either of the following criteria are met in the DLT assessment period:

- The patient experienced a DLT at any time after initiation of the first infusion of magrolimab.
- The patient did not experience a DLT and completed at least 3 infusions of magrolimab (28-day cycle), and at least 2 doses of nab-paclitaxel or paclitaxel in Safety Run-in Cohort 1.

DLT Assessment Period for Safety Run-in Cohort 2: The DLT assessment period will be the first cycle (21 days). Patients are considered evaluable for assessment of a DLT if either of the following criteria are met in the DLT assessment period:

- The patient experienced a DLT at any time after initiation of the first infusion of magrolimab.
- The patient did not experience a DLT and completed at least 2 infusions of magrolimab (21-day cycle), and at least 2 infusions of sacituzumab govitecan in Safety Run-in Cohort 2.

If a patient experiences a DLT during the DLT assessment period, the patient will discontinue treatment. Though the dosing during maintenance cycles is higher, the total dose given during the priming cycle is higher than the maintenance dose. However, the totality of the data on safety during a longer follow-up will be taken into consideration when RP2D is determined.

Patients who are not evaluable for DLT assessment in the Safety Run-in Cohorts will be replaced.

3.1.1.2. DLT Definition

All toxicities will be graded according to the NCI CTCAE, Version 5.0 (Appendix 4).

A DLT is defined as any:

- Grade 3 or higher hematologic toxicity including
  - Grade 3 hemolytic anemia that is medically significant, requiring hospitalization or prolongation of existing hospitalization, disabling, or limiting self-care activities of daily life.

- Event meeting Hy's Law criteria (Section 7.7).

- Grade 3 or higher nonhematologic toxicity that has worsened in severity from pretreatment baseline during the DLT assessment period, and in the opinion of the investigator, the AE is at least possibly related to magrolimab.

The following are exceptions to the DLT definition and are NOT considered a DLT:

- Grade 3 anemia; however, Grade 3 hemolytic anemia that is medically significant is considered a DLT (see above).

- Grade 3 febrile neutropenia that has responded clinically within 72 hours of maximal supportive care.

- Grade 3 neutropenia that resolves to Grade 2 or pretreatment baseline with supportive care (including growth factors) within 21 days or Grade 4 neutropenia lasting for 7 days or less with supportive measures.

- Grade 3 thrombocytopenia in the absence of clinically significant bleeding that resolves to Grade 2 or pretreatment/baseline within 21 days.

- Grade 3 indirect/unconjugated hyperbilirubinemia that resolves to Grade 2 or lower with supportive care within 1 week and is not associated with other clinically significant consequences.

- Grade 3 electrolyte abnormalities that improve to Grade 2 or lower or baseline within 72 hours, are not clinically complicated, and resolve spontaneously or respond to conventional medical interventions.

- Grade 3 transaminase elevations characterized by increases of more than 5 to less than 8 times the upper limit of normal (ULN) for AST and/or alanine aminotransferase (ALT). A Grade 3 transaminase elevation should meet DLT criteria for increases of more than 8 ULN for AST/ALT lasting less than 7 days. Grade 3 elevation in alkaline phosphatase that resolves to Grade 2 or lower with supportive care within 1 week and is not associated with other clinically significant consequences.

- Grade 3 nausea/vomiting, or diarrhea that resolves to Grade 2 or lower within 72 hours with adequate antiemetic and other supportive care.

- Grade 3 fatigue that resolves to Grade 2 or lower within 1 week on study.

- Grade 3 magrolimab, nab-paclitaxel, paclitaxel, and sacituzumab govitecan IRRs in the absence of an optimal pretreatment regimen as defined in Section 7.8.1.3.

- Grade 3 tumor lysis syndrome or electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia) that resolve to Grade 2 or lower or baseline within 72 hours.

- Grade 3 hypomagnesemia that resolves to Grade 2 or lower within 1 week.
- Grade 3 or 4 lymphopenia or leukopenia not associated with other clinically significant consequences.
- Transient (less than or equal to 48 hours) Grade 3 local reactions, flu-like symptoms, myalgias, fever, headache, acute pain, or skin toxicity that resolves to Grade 2 or lower within 72 hours after medical management (eg, supportive care, including immunosuppressant treatment) has been initiated.

The recommended dose for Phase 2 Cohort 1 and Phase 2 Cohort 2 will be determined by the sponsor based on all relevant clinical and PK data from all patients treated in the Safety Run-in phase.

3.1.1.3. Safety Review Team

An SRT will be established to assess safety of the patients.

The SRT will include at least 1 investigator, a Gilead safety physician, and the Gilead medical monitor. Others may be invited to participate as members of the SRT if additional expertise is desired. The medical monitor serves as the chair of the SRT. An SRT charter (or similar document) will be agreed on by all SRT members prior to the first SRT meeting. The data reviewed at the SRT meeting to make decisions will be defined in the SRT charter (or similar document). The quality control checks performed on the data reviewed and used for making decisions will be described in the SRT charter (or similar document).

3.1.2. Phase 2 Cohorts

Phase 2 Cohort 1

Once Safety Run-in Cohort 1 is completed and the RP2D for magrolimab + nab-paclitaxel or paclitaxel is determined, the sponsor will open Phase 2 Cohort 1. In this open-label, randomized, 2-arm cohort, unresectable, locally advanced or mTNBC patients will be randomized in a 1:1 ratio to either magrolimab + nab-paclitaxel or paclitaxel (Experimental Arm A) or nab-paclitaxel or paclitaxel (Control Arm B).

The primary efficacy assessment will be investigator-assessed PFS. In the original study design, the primary analysis was to occur after 63 events; however, due to the early closure of Phase 2 Cohort 1, the primary analysis will occur when every enrolled patient has a minimum of 6 months follow-up. Stratification factors for randomization include the following:

- Receipt versus nonreceipt of neoadjuvant and/or adjuvant taxane therapy.
- Presence versus absence of liver metastases.
- Treatment with nab-paclitaxel versus paclitaxel.

Phase 2 Cohort 2

Once Safety Run-in Cohort 2 is completed and the RP2D for magrolimab + sacituzumab govitecan is determined, the sponsor will open enrollment in Phase 2 Cohort 2. In this open-label single-arm cohort, unresectable, locally advanced or mTNBC patients will receive magrolimab in combination with sacituzumab govitecan.

3.1.2.1. Treatment-Related Toxicity Monitoring

Treatment-related toxicity will be monitored by a Gilead Data Review Committee (GDRC) at a preset frequency with the stopping boundary listed in Table 2 after the safety data of the first 12 treated patients in Phase 2 Cohort 1 Arm A from at least 1 cycle of follow-up become available. From the original design where 46 patients were planned to be enrolled for Phase 2 Cohort 2 Arm A, a second GDRC review was planned when safety data of 36 patients from the first 3 cycles of follow-up become available. Given the early closure of Phase 2 Cohort 1, a total of 14 patients have been enrolled for Phase 2 Cohort 2 Arm A; therefore, only the first GDRC at N = 12 will occur. The ongoing treatment will stop when the number of patients with either Grade 4 or 5 treatment-related treatment-emergent adverse events (TEAEs) or treatment-related deaths meet the criteria. Bayesian toxicity monitoring {Lee 2021} based on beta-binomial model was used to derive the boundaries. Noninformative prior distribution of Beta (0.5, 0.5) for the true toxicity rate (θ) of Grade 4 or 5 treatment-related TEAEs is used, and excessive toxicity can be claimed when $P(\theta \geq 0.18|n, r) \geq 0.9$. The 'n' and 'r' are the sample size and number of patients with specific events at the interim analysis for toxicity monitoring, respectively. Maximum toxicity rate was assumed at 18%, where the excessive toxicity can be claimed if the posterior probability of excessive toxicity is higher than or equal to threshold at 90%. The probabilities of early stopping are 2.6%, 15.5%, and 50.8% when the true rates are 10%, 18%, and 30%, respectively. Similarly, noninformative prior distribution of Beta (0.25, 0.25) for the true toxicity rate of treatment-related death is used with maximum toxicity rate and threshold assumed as 2.5% and 90%, respectively. The probabilities of early stopping are 0.6%, 3.5%, and 11.8 % when the true rates are 1%, 2.5%, and 5%, respectively. For Phase 2 Cohort 2, treatment-related toxicity will be monitored by GDRC at a preset frequency with stopping boundary listed in Table 3 after the first 10 patients are treated at the dose level for Phase 2 Cohort 2 for at least 1 cycle of follow-up, and thereafter when safety data from 30 patients from the first 3 cycles of follow-up become available. Same prior distribution as above are assumed. For Grade 4 or 5 treatment-related TEAEs, maximum toxicity rate and threshold are assumed as 40% and 90%, respectively. The probabilities of early stopping are 2.0%, 21.1%, and 73.1% when the true rates are 25%, 40%, and 55%, respectively. For treatment-related deaths, maximum toxicity rate and threshold are assumed as 2.5% and 90%, respectively. The probabilities of early stopping are 0.7%, 5.2%, and 21.5% when the true rates are 1%, 2.5%, and 5% respectively.

Table 2. Stopping Boundary Due to Toxicity (Phase 2 Cohort 1 Arm A)

	N = 12
Grade 4 or 5 treatment-related TEAEs	≥ 4
Treatment-related deaths	≥ 2

TEAEs = treatment-emergent adverse events

Table 3. Stopping Boundary Due to Toxicity (Phase 2 Cohort 2)

	N = 10	N = 30
Grade 4 or 5 treatment-related TEAEs	≥ 6	≥ 16
Treatment-related deaths	≥ 2	≥ 3

TEAEs = treatment-emergent adverse events

3.2. Study Treatments

3.2.1. Safety Run-in Cohort 1 and Phase 2 Cohort 1

Table 4 shows the study treatments for Safety Run-in Cohort 1 and Table 5 shows the study treatments for Phase 2 Cohort 1. The schedules of assessments are provided in Appendix Table 1 and Appendix Table 3. Nab-paclitaxel or paclitaxel use will be per investigator discretion and in accordance with local guidelines and practices.

Table 4. Safety Run-in Cohort 1: Dose Level, Schedule, and De-escalation

Drug	Dose Level	Dose Schedule (Cycles are 28 Days)		
		Cycle 1	Cycle 2	Cycle 3+
Magrolimab	Starting dose 30 mg/kg	1 mg/kg IV (3 h ± 30 min) on Day 1 (priming dose); 30 mg/kg IV (2 h ± 30 min) on Days 8, 15, and 22	30 mg/kg IV (2 h ± 30 min) on Days 1, 8, 15, and 22	30 mg/kg IV (2 h ± 30 min) on Days 1 and 15
	De-escalation Level −1 20 mg/kg	1 mg/kg IV (3 h ± 30 min) on Day 1 (priming dose); 20 mg/kg IV (2 h ± 30 min) on Days 8, 15, and 22	20 mg/kg IV (2 h ± 30 min) on Days 1, 8, 15, and 22	20 mg/kg IV (2 h ± 30 min) on Days 1 and 15
	De-escalation Level −2 15 mg/kg	1 mg/kg IV (3 h ± 30 min) on Day 1 (priming dose); 15 mg/kg IV (2 h ± 30 min) on Days 8, 15, and 22	15 mg/kg IV (2 h ± 30 min) on Days 1, 8, 15, and 22	15 mg/kg IV (2 h ± 30 min) on Days 1 and 15
Nab-paclitaxel	100 mg/m^2	100 mg/m^2 IV on Days 1, 8, and 15	100 mg/m^2 IV on Days 1, 8, and 15	100 mg/m^2 IV on Days 1, 8, and 15
Paclitaxel	90 mg/m^2	90 mg/m^2 IV on Days 1, 8, and 15	90 mg/m^2 IV on Days 1, 8, and 15	90 mg/m^2 IV on Days 1, 8, and 15

IV = intravenous

Table 5. Phase 2 Cohort 1: Dose Level and Schedule

Drug	Dose Schedule (Cycles are 28 Days)		
	Cycle 1	Cycle 2	Cycle 3+
Magrolimab (Arm A only) 1 mg/kg IV (3 h ± 30 min)	Day 1 (priming dose)		
Magrolimab (Arm A only) RP2D[a] IV (2 h ± 30 min)	Days 8, 15, and 22	Days 1, 8, 15, and 22	Days 1 and 15
Nab-paclitaxel (Arms A and B) 100 mg/m^2 IV	Days 1, 8, and 15	Days 1, 8, and 15	Days 1, 8, and 15
Paclitaxel (Arms A and B) 90 mg/m^2 IV	Days 1, 8, and 15	Days 1, 8, and 15	Days 1, 8, and 15

IV = intravenous; RP2D = recommended Phase 2 dose
a RP2D as determined in the Safety Run-in Cohort.

3.2.2. Safety Run-in Cohort 2 and Phase 2 Cohort 2

Table 6 shows the study treatments for Safety Run-in Cohort 2 and Table 7 shows the study treatments for Phase 2 Cohort 2. The schedules of assessments are provided in Appendix Table 2 and Appendix Table 3.

Table 6. Safety Run-in Cohort 2: Dose Level, Schedule, and De-escalation

Drug	Dose Level	Dose Schedule (Cycles are 21 Days)		
		Cycle 1	Cycle 2	Cycle 3+
Magrolimab	Starting dose 30 mg/kg	1 mg/kg IV (3 h ± 30 min) on Day 1 (priming dose); 30 mg/kg IV (2 h ± 30 min) on Days 8 and 15	30 mg/kg IV (2 h ± 30 min) on Days 1, 8, and 15	60 mg/kg IV (2 h ± 30 min) on Day 1
	De-escalation Level −1 20 mg/kg	1 mg/kg IV (3 h ± 30 min) on Day 1 (priming dose); 20 mg/kg IV (2 h ± 30 min) on Days 8 and 15	20 mg/kg IV (2 h ± 30 min) on Days 1, 8, and 15	45 mg/kg IV (2 h ± 30 min) on Day 1
	De-escalation Level −2 15 mg/kg	1 mg/kg IV (3 h ± 30 min) on Day 1 (priming dose); 15 mg/kg IV (2 h ± 30 min) on Days 8 and 15	15 mg/kg IV (2 h ± 30 min) on Days 1, 8, and 15	30 mg/kg IV (2 h ± 30 min) on Day 1
Sacituzumab govitecan	10 mg/kg	10 mg/kg IV (3 h ± 30 min) on Day 1 and 10 mg/kg IV (1 to 2 h ± 30 min) on Day 8	10 mg/kg IV (1 to 2 h ± 30 min) on Days 1 and 8	10 mg/kg IV (1 to 2 h ± 30 min) on Days 1 and 8

IV = intravenous

Table 7. Phase 2 Cohort 2: Dose Level and Schedule

Drug	Dose Schedule (Cycles are 21 Days)		
	Cycle 1	Cycle 2	Cycle 3+
Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1 (priming dose)		
Magrolimab RP2D[a] IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	Day 1
Sacituzumab govitecan 10 mg/kg IV	Day 1 (3 h ± 15 min) and Day 8 (1 to 2 h ± 30 min)	Days 1 and 8 (1 to 2 h ± 30 min)	Days 1 and 8 (1 to 2 h ± 30 min)

IV = intravenous; RP2D = recommended Phase 2 dose
a RP2D as determined in the Safety Run-in Cohort.

For patients receiving magrolimab in combination with paclitaxel/nab-paclitaxel (Safety Run-in Cohort 1 and Cohort 1, Arm A) or sacituzumab govitecan (Safety Run-in Cohort 2 and Cohort 2), Cycle 1 Day 1 treatment can be administered over 2 days such that magrolimab is administered on Cycle 1 Day 1 and paclitaxel/nab-paclitaxel or sacituzumab govitecan on Cycle 1 Day 2. This also applies to repriming cycles that require Cycle 1 Day 1 dosing of magrolimab. Cycle 1 Day 1 dosing and infusion time requirements for each agent should be followed, as listed in Table 4, Table 5, Table 6, and Table 7. Premedication guidelines should be followed prior to magrolimab (see Section 5.8), paclitaxel/nab-paclitaxel (see Section 5.11), or sacituzumab govitecan (see Section 5.14). Patients should be observed during and following infusion for signs or symptoms of IRRs (see Section 5.6 for magrolimab, Section 5.10 for paclitaxel/nab-paclitaxel, and Section 5.13 for sacituzumab govitecan).

3.3. Duration of Treatment

Cycle lengths are 28 days for Safety Run-in Cohort 1 and Phase 2 Cohort 1. Cycle lengths are 21 days for Safety Run-in Cohort 2 and Phase 2 Cohort 2. Patients may continue treatment unless they develop unacceptable toxicity that cannot be clinically managed by dose or schedule modifications.

If in the opinion of the investigator, the patient is deriving a clinical benefit, magrolimab, nab-paclitaxel, paclitaxel, or sacituzumab govitecan may be continued if the combination partner is discontinued due to unacceptable toxicity:

- Magrolimab can be continued if nab-paclitaxel, paclitaxel, or sacituzumab govitecan is discontinued for unacceptable toxicity.
- Nab-paclitaxel, paclitaxel, or sacituzumab govitecan can be continued if magrolimab is discontinued for unacceptable toxicity.

Patients who discontinue all study drugs will be followed for safety, disease progression, and survival.

During the study, patients who meet criteria for disease progression per RECIST, Version 1.1, and show evidence of a clinical benefit may continue study drug treatment past the initial determination of disease progression, provided all of the following criteria are met:

- No new symptoms or worsening of previous symptoms
- Tolerance of study treatment
- Stable Eastern Cooperative Oncology Group (ECOG) performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (for example, CNS metastases)

The decision to continue treatment should be approved by the sponsor. Patients who continue study drug treatment past the initial determination of disease progression will be required to reconsent to the continued treatment.

3.4. Discontinuation Criteria

Reasons for discontinuation of study treatment may include, but are not limited to, the following:

- Disease progression (treatment beyond disease progression is allowed per criteria in Section 3.3)
- Unacceptable toxicity
- Loss of clinical benefit
- Clinically significant change in the patient's status that precludes further treatment (eg, pregnancy [see Section 7.4.2.3] or other AEs)
- Patients who permanently discontinue study drug for pregnancy should continue to have assessments for early discontinuation from the study performed (see Section 6.11); if there are any questions regarding permanent discontinuation, these should be discussed with the sponsor
- Patient request, with or without a stated reason
- Patient noncompliance
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board (IRB) or independent ethics committee (IEC)
- Investigator or treating physician decision in the absence of any of the above

Patients may continue study drug treatment beyond disease progression in accordance with criteria in Section 3.3. All patients must be followed through completion of all study treatment.

3.5. Discontinuation From Study Criteria/End of Study

All Patients: The end of the entire study for all patients is defined as the date on which the last patient remaining on study completes the last study visit/call or when the sponsor decides to end the study. The sponsor reserves the right to terminate the study at any time for any reason (including safety).

Individual Patients: Patients are considered to have completed study participation altogether when they are no longer followed for survival.

All patients will be followed for survival until death, withdraw from consent, lost to follow-up, and the end of study, whichever occurs first.

For any patient who dies during this follow-up period, the immediate cause of death must be reported to the sponsor.

3.6. Poststudy Care

Upon withdrawal from study treatment, patients will receive the care upon which they and their physicians agree. Patients will be followed for disease progression (if applicable), survival, and AEs as specified in Appendix Table 3.

3.7. Source Data

The source data for this study will be obtained from original records (eg, clinic notes, hospital records, patient charts), central laboratory, local laboratory, and/or specialty laboratory (for PK, ADA, and/or PD data) and/or additional biomarker testing, and interactive response technology (IRT).

3.8. Biomarker Samples to Address the Study Objectives

Peripheral blood and tumor biopsy samples will be collected from all patients who have provided consent to participate in this study. They may be used to evaluate the association of systemic and/or tissue-based biomarkers with study drug response, including efficacy and/or AEs, dosage selection, and to better understand the biology of the cancer indications studied, as well as the efficacy and MOA for magrolimab combinations. 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 described below. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon new state-of-the-art knowledge.

Biomarker assessments will include:

- Blood sample for RO at select sites
- Peripheral blood mononuclear cell (PBMC) to assess immune cell phenotypes (at select sites)

- Serum and plasma biomarker samples for the analysis of circulating factors such as cytokines, soluble immune receptors, and antibodies
- Whole blood RNA samples for leukocyte gene expression analysis
- Immunophenotyping assay
- T-cell receptor sequencing sample to assess immune repertoire changes
- Circulating tumor DNA sample to monitor treatment response
- Stool samples to assess microbiome
- Mandatory baseline tumor tissue and on-treatment biopsies to assess immune cells, tumor cell-surface proteins, Trop-2 expression, and/or genomic biomarkers

Blood and tumor biopsy samples will be collected to measure biomarkers, which may include but will not be limited to the presence of or changes to immune cell populations, secreted protein factors, the expression of cell-surface markers on either tumor cells or cells of the tumor microenvironment, and genetic mutations in tumor cells or subclones of tumor cells, at the time points listed in the schedule of assessments (Appendix Table 4).

Blood and tumor samples will also be used for genomic research. In addition, a whole blood sample will be collected at Cycle 1 Day 1 but may be collected at any time during the study, if necessary. These samples will be used to identify or validate genetic markers that may increase our knowledge and understanding of the biology of the study disease and related diseases and to study the association of genetic markers with disease pathogenesis, progression, and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. These specimens may also be used to develop biomarker or diagnostic assays and establish the performance characteristics of these assays. Genomics research may include sequencing of genetic material derived from both cancer cells and normal cells. Sequencing of genetic material derived from cancer cells will be used to better understand the MOA of magrolimab combinations in this patient population and to potentially to identify subsets of patients who are likely to benefit. Sequencing of genetic material derived from normal cells will be used to define differences in sequence that are cancer specific.

Samples collected for biomarker assessments will be destroyed no later than 15 years after the end of study or per country requirements.

3.8.1. CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

[redacted]

4. PATIENT POPULATION

4.1. Number of Patients and Patient Selection

Approximately 104 patients may be enrolled in the study:

- Safety Run-in Cohort 1: approximately 6 to 18 patients
- Phase 2 Cohort 1: approximately 28 patients
- Safety Run-in Cohort 2: approximately 6 to 18 patients
- Phase 2 Cohort 2: approximately 40 patients

Patients enrolled in Cohort 1 Arm B with documented progressive disease can rescreen to enroll in Cohort 2 as long as they meet all other eligibility criteria.

4.1.1. Patient Replacement

Patients may be replaced during the Safety Run-in Cohort if not evaluable for DLT assessment as described in Section 3.1.1.1.

4.2. Inclusion Criteria

All patients must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Patient has provided informed consent.
2) Patient is willing and able to comply with clinic visits and procedures outlined in the study protocol.
3) Male or female, at least 18 years of age.
4) Patients must have an ECOG performance status of 0 or 1.
5) Laboratory measurements, blood counts:
    a) Hemoglobin must be ≥ 9 g/dL prior to initial dose of study treatment. RBC transfusions are allowed to meet hemoglobin eligibility within limits set per Exclusion Criterion #4 (and per Section 7.8.1.2), except in South Korea.
    b) Absolute neutrophil count (ANC) at least 1.5×10^9/L without growth factor support within 2 weeks of study treatment initiation.
    c) Platelets at least 100×10^9/L.

6) Laboratory measurements, renal function:

   a) Patients must have adequate renal function as demonstrated by a creatinine clearance of at least 30 mL/min; calculated by the Cockcroft Gault formula.

7) Adequate liver function, as demonstrated by:

   a) AST less than or equal to 2.5 × ULN or less than or equal to 5 × ULN in patients with liver metastases.

   b) ALT less than or equal to 2.5 × ULN or less than or equal to 5 × ULN in patients with liver metastases.

   c) Bilirubin less than or equal to 1.5 × ULN, or less than or equal to 3.0 × ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or genetic equivalent.

8) Pretreatment blood cross-match completed (Section 7.8.1.1).

9) Male and female patients of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 5.

10) Measurable disease according to RECIST, Version 1.1. Previously irradiated lesions can be considered as measurable disease only if disease progression has been unequivocally documented at that site since radiation.

11) Patients must have a life expectancy of 3 months or greater, in the opinion of the investigator.

Safety Run-in Cohort 1 and Phase 2 Cohort 1

In addition to meeting the inclusion criteria for all patients, patients who are enrolled into Safety Run-in Cohort 1 and Phase 2 Cohort 1 must fulfill the following cohort-specific inclusion criteria:

12) Patients previously untreated with systemic therapy for unresectable locally advanced or metastatic breast cancer and with a diagnosis of TNBC that is histologically or cytologically confirmed based on the most recent analyzed biopsy or other pathology specimen, defined as negative for estrogen receptor (ER), PR, and HER2 according to the most recent American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guideline (Appendix 9).

13) Patients whose tumors are considered PD-L1 negative, as determined by an approved test according to local standards.

14) Prior systemic treatment for neoadjuvant and/or adjuvant therapy and/or curative intent radiation therapy is permitted if completed at least 6 months prior to enrollment.

Note: Maintenance therapies are not counted as separate lines of therapy.

Safety Run-in Cohort 2 and Phase 2 Cohort 2

In addition to meeting the inclusion criteria for all patients, patients who are enrolled into Safety Run-in Cohort 2 and Phase 2 Cohort 2 must fulfill the following cohort-specific inclusion criterion:

15) Patients with unresectable, locally advanced or metastatic breast cancer with a diagnosis of TNBC that is histologically or cytologically confirmed based on the most recent analyzed biopsy or other pathology specimen, defined as negative for ER, PR, and HER2 according to the most recent ASCO/CAP guideline (Appendix 9), who have received at least 1 and no more than 2 prior lines of systemic therapy in the unresectable, locally advanced/metastatic setting. Patients must have been previously treated with a taxane in the neoadjuvant, adjuvant, or locally advanced/metastatic setting.

16) Patients with tumors considered positive for PD-L1 expression (as determined by an approved test according to local standards) must have received an immune checkpoint inhibitor for prior line of treatment for locally advanced/metastatic disease.

4.3. Exclusion Criteria

Patients who meet *any* of the following exclusion criteria are not to be enrolled in this study:

1) Positive serum pregnancy test.

2) Breastfeeding female.

3) Active CNS disease. Patients with asymptomatic and stable, treated CNS lesions who have been off steroids, radiation and/or surgery, and/or other CNS-directed therapy for at least 4 weeks are allowed.

4) RBC transfusion dependence, defined as requiring more than 2 units of packed RBC transfusions during the 4-week period prior to screening. Red blood cell transfusions are permitted during the screening period and prior to enrollment to meet the hemoglobin inclusion criteria, except in South Korea.

5) History of hemolytic anemia, autoimmune thrombocytopenia, or Evans syndrome in the last 3 months.

6) Known hypersensitivity to any of the study drugs, the metabolites, or formulation excipient.

7) Prior treatment with CD47 or signal regulatory protein alpha-targeting agents.

8) Current participation in another interventional clinical study. Patients enrolled in a clinical study who are no longer receiving therapeutic intervention are eligible.

9) Known inherited or acquired bleeding disorders.

10) Significant disease or medical conditions, as assessed by the investigator and sponsor, that would substantially increase the risk:benefit ratio of participating in the study. This includes, but is not limited to, acute myocardial infarction within the last 6 months, unstable angina, uncontrolled diabetes mellitus, significant active infections, and congestive heart failure New York Heart Association Class III-IV. Additional information for sites in the United Kingdom (UK) is provided in Appendix 12.

11) Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancies for which patients are not on active anticancer therapies and who are in complete remission for over 2 years.

12) Known active or chronic hepatitis B or C infection or human immunodeficiency virus infection in medical history.

13) Uncontrolled pleural effusion.

14) Uncontrolled hypercalcemia (Grade 2 or higher) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy.

15) Rapid deterioration during screening prior to enrollment (eg, significant change in performance status, 20% or greater decrease in serum albumin levels or uncontrolled tumor-related pain).

16) Severe/serious systemic infection within 4 weeks of randomization or any active, uncontrolled infection requiring systemic therapy within 7 days of enrollment.

17) Other concurrent medical or psychiatric conditions that, in the investigator's opinion, may be likely to confound study interpretation or prevent completion of study procedures and follow-up examinations.

18) Prior anticancer therapy within the specified timeframe prior to start of magrolimab is not permitted: 2 weeks for chemotherapy agents, endocrine therapy, or targeted small molecule therapy; 3 weeks for monoclonal antibodies, antibody-drug conjugates, immunotherapy, or investigational agents.

19) Patients who have received a live vaccine within 30 days of randomization.

Safety Run-in Cohort 1 and Phase 2 Cohort 1

Patients who meet the following exclusion criterion are not eligible to be enrolled into Safety Run-in Cohort 1 or Phase 2 Cohort 1:

20) Disease progression within 6 months following neoadjuvant/adjuvant therapy or prior lines of systemic therapy for unresectable locally advanced or metastatic breast cancer.

NOTE: Localized non-CNS radiotherapy, hormonal therapy for breast cancer in the curative setting, and treatment with bisphosphonates and receptor activator of nuclear factor kappa B ligand inhibitors are not included in Exclusion Criterion #20. Patients should be recovered from the effects of radiation. Additional information for sites in the UK is provided in Appendix 12

Safety Run-in Cohort 2 and Phase 2 Cohort 2

Patients who meet *any* of the following exclusion criteria are not eligible to be enrolled into Safety Run-in Cohort 2 or Phase 2 Cohort 2:

21) Patients with active chronic inflammatory bowel disease (ulcerative colitis, Crohn disease) and patients with a history of bowel obstruction or gastrointestinal perforation within 6 months of enrollment.

22) Patients who previously received topoisomerase I inhibitors or antibody-drug conjugates containing a topoisomerase I inhibitor.

23) High-dose systemic corticosteroids (≥ 20 mg of prednisone or its equivalent) are not allowed within 2 weeks of Cycle 1 Day 1.

24) Have not recovered (ie, ≥ Grade 2 is considered not recovered) from AEs due to a previously administered agent.

    — Note: patients with any grade of neuropathy, alopecia, hypo- or hyperthyroidism, or other endocrinopathies that are well controlled with hormone replacement are an exception to this criterion and will qualify for the study.

    — Note: if patients received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

NOTE: Localized non-CNS radiotherapy is not criteria for exclusion. Patients should be recovered from the effects of radiation.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding, and Treatment Codes Access

5.1.1. Randomization

Patients in Phase 2 Cohort 1 who meet eligibility criteria will be randomized in a 1:1 ratio to magrolimab in combination with nab-paclitaxel or paclitaxel or either nab-paclitaxel or paclitaxel using IRT. Nab-paclitaxel or paclitaxel use will be per investigator discretion and in accordance with local guidelines and practices. The first dose on Day 1 must be within 3 days of randomization.

Randomization will be stratified by 1) receipt versus nonreceipt of neoadjuvant and/or adjuvant taxane therapy, 2) presence versus absence of liver metastases, and 3) treatment with nab-paclitaxel versus paclitaxel.

5.1.2. Blinding

Blinding of treatment assignments or data will not be performed in this study.

5.2. Description and Handling of Magrolimab

5.2.1. Formulation

Magrolimab is formulated as a sterile, clear, preservative-free liquid intended for IV administration containing 10 mM sodium acetate, 5% weight-to-volume ratio (w/v) sorbitol, 0.01% w/v polysorbate 20 at pH of 5.0. Each vial is manufactured to ensure a deliverable volume of 10 mL containing 200 mg of magrolimab at a concentration of 20 mg/mL.

5.2.2. Packaging and Labeling

Magrolimab is supplied in single-use, 10-mL glass vials with coated elastomeric stoppers and aluminum crimp overseals with a flip-off cap.

Study drug(s) to be distributed by the sponsor 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) for Clinical Trials Directive, or Annex 6 for Clinical Trials Regulation, as applicable, and/or other local regulations.

5.2.3. Storage and Handling

Magrolimab should be stored at 2 °C to 8 °C (36 °F to 46 °F). Magrolimab should not be frozen. Protect from light during storage. Do not shake. Storage conditions are specified on the label. Until dispensed to the patients, 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. Description and Handling of Nab-paclitaxel

5.3.1. Formulation

Nab-paclitaxel is commercially sourced. Information regarding the formulation can be found in the current local prescribing information.

5.3.2. Packaging and Labeling

Commercial product of nab-paclitaxel will be used for this study. Study drug(s) to be distributed by the sponsor 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. Alternatively, in alignment with local regulations commercial product may be sourced locally by the sites.

5.3.3. Storage and Handling

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

5.4. Description and Handling of Paclitaxel

5.4.1. Formulation

Paclitaxel is commercially sourced. Information regarding the formulation can be found in the current local prescribing information.

5.4.2. Packaging and Labeling

Commercial product of paclitaxel will be used for this study. Study drug(s) to be distributed by the sponsor 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. Alternatively, in alignment with local regulations commercial product may be sourced locally by the sites.

5.4.3. Storage and Handling

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

5.5. Description and Handling of Sacituzumab Govitecan

5.5.1. Formulation

Sacituzumab govitecan is supplied as a sterile, off-white to yellowish lyophilized powder in single-dose glass vials. It is formulated in 2-(N-morpholino) ethane sulfonic acid buffer containing trehalose and polysorbate 80 and contains no preservatives. Following reconstitution, the concentration of the study drug is 10 mg/mL. The pH of the reconstituted solution is approximately 6.5.

5.5.2. Packaging and Labeling

Sacituzumab govitecan is packaged in single-use, 50R, glass vials, closed with coated elastomeric stoppers and capped with flip-off caps with aluminum overseals. Study drug(s) to be distributed by the sponsor 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.

5.5.3. Storage and Handling

Sacituzumab govitecan vials must be stored in a refrigerator at 2 °C to 8 °C (36 °F to 46 °F) in the original carton to protect from light until time of reconstitution. Since the formulated drug product contains no preservative, the vials are single-use only.

Refer to the current version of the Pharmacy Manual for additional details.

5.6. Dosage and Administration of Magrolimab

Magrolimab should be administered as outlined in the Pharmacy Manual for the study. The dose of magrolimab will be calculated based on actual weight enrollment (using weight obtained either at screening or on Day 1) and will remain constant throughout the study unless there is a more than 10% change in weight from baseline. Modifications to the study drug doses administered should be made for a more than 10% change in body weight and/or according to local and regional prescribing standards. Dose modifications for changes in body weight less than 10% may be made according to local institutional guidelines.

The duration for the first magrolimab (priming) infusion will be 3 hours (± 30 minutes). For subsequent doses, the magrolimab (maintenance) infusion will be 2 hours (± 30 minutes). The reduced infusion time to 2 hours is utilized based on prior data demonstrating majority CD47 RO on peripheral blood cells, thus mitigating anticipated RBC toxicities from magrolimab.

Magrolimab doses will be given weekly during Cycles 1 and 2 and every 2 weeks (Cohort 1) or every 3 weeks (Cohort 2) during Cycle 3 and beyond depending on the dose of magrolimab. **Magrolimab doses are not to be given on consecutive days**.

When magrolimab is given in combination with nab-paclitaxel, paclitaxel, or sacituzumab govitecan, magrolimab should be infused first. All patients should be monitored for 1 hour after infusion for priming, repriming, and maintenance doses during Cycle 1. Postinfusion monitoring should begin after the infusion is complete but prior to administering nab-paclitaxel, paclitaxel, or sacituzumab govitecan. Postinfusion monitoring is not required for doses after Cycle 1 Day 22. Patients who experience any treatment-emergent AEs during the observation period should be further monitored, as clinically appropriate. Refer to Section 7.8.1.2 for postinfusion hemoglobin reporting requirements.

For patients receiving magrolimab in combination with paclitaxel/nab-paclitaxel (Safety Run-in Cohort 1 and Cohort 1, Arm A) or sacituzumab govitecan (Safety Run-in Cohort 2 and Cohort 2), Cycle 1 Day 1 treatment can be administered over 2 days such that magrolimab is administered on Cycle 1 Day 1 and paclitaxel/nab-paclitaxel or sacituzumab govitecan on Cycle 1 Day 2. This also applies to repriming cycles that require Cycle 1 Day 1 dosing of magrolimab. Cycle 1 Day 1 dosing and infusion time requirements for each agent should be followed, as listed in Table 4, Table 5, Table 6, and Table 7. Premedication guidelines should be followed prior to magrolimab (see Section 5.8), paclitaxel/nab-paclitaxel (see Section 5.11), or sacituzumab govitecan (see Section 5.14). Patients should be observed during and following the infusion for signs or symptoms of IRRs (see Section 5.10 for paclitaxel/nab-paclitaxel and Section 5.13 for sacituzumab govitecan).

Patients may continue study treatment until they show evidence of disease progression, relapse, loss of clinical benefit, or unacceptable toxicity (further details about treatment discontinuation are in Section 3.4).

5.6.1. Treatment Delay and Repriming for Magrolimab

Given the large CD47 antigen sink on normal cells, patients who have a long dose delay of magrolimab are required to be reprimed with magrolimab dosing to resaturate the CD47 antigen sink. Guidelines for repriming/re-escalation for magrolimab after a dose delay are provided in Section 5.7.

The magrolimab dosing regimens for each cohort are described in Table 4 (Safety Run-in Cohort 1), Table 5 (Phase 2 Cohort 1), Table 6 (Safety Run-in Cohort 2), and Table 7 (Phase 2 Cohort 2).

5.7. Dose Modifications, Delays, and Discontinuation for Magrolimab

In most circumstances, the dose of magrolimab should not be reduced except in the Safety Run-in Cohorts in the case of dose de-escalation based on DLTs.

Clinical safety and PK data from dose-finding studies in both solid tumor and hematologic malignancies have not demonstrated any dose-dependent toxicities associated with magrolimab. Dose reduction of magrolimab may be allowed in certain circumstances (eg, with certain AEs), consultation with the sponsor is recommended prior to dose reductions of magrolimab.

When the combination drugs (nab-paclitaxel or paclitaxel or sacituzumab govitecan) are delayed due to toxicities, magrolimab should continue independently as per magrolimab administration schedule. Continuous dosing of magrolimab is needed to maintain efficacious exposures and optimal efficacy. During the maintenance phase (Cycle 3 onwards), if the last dose of magrolimab was administered within the previous 7 to 13 days (Cohort 1) or within the previous 10 to 20 days (Cohort 2), the subsequent magrolimab dose may be administered earlier than scheduled in order to synchronize with the backbone chemotherapy administration.

Magrolimab should be withheld if treatment-emergent and/or related AEs occur. In the event of magrolimab delay, dosing should resume as soon as it is clinically appropriate and logistically possible, without waiting to align with the patient's original treatment schedule.

The repriming guidelines shown in Table 8 (Safety Run-in Cohort 1 and Phase 2 Cohort 1) and in Table 9 (Safety Run-in Cohort 2 and Phase 2 Cohort 2) should be followed for patients with dose delays. During repriming, cycle numbering and efficacy, biomarker, PK, and immunogenicity assessments should continue according to the assigned cycle number. If repriming is required during Cycles 1 or 2, dosing frequency and safety assessments should follow Cycle 1, then Cycle 2, and begin maintenance from Cycle 3 onwards. If repriming is required during the maintenance phase (Cycle 3 onwards), dosing frequency and safety assessments should follow Cycle 1 and subsequent dosing should resume maintenance dosing at the next assigned cycle.

When magrolimab safety assessments and dosing schedule should follow the Cycle 1 assessments, refer to Table 4 (Safety Run-in Cohort 1), Table 5 (Phase 2 Cohort 1), Table 6 (Safety Run-in Cohort 2), and Table 7 (Phase 2 Cohort 2). When magrolimab safety assessments and dosing schedule are to be switched back to the next assigned cycle schedule, refer to Appendix Table 1 and Appendix Table 2. If repriming is required during Cycles 1 or 2, dosing frequency and safety assessments should follow Cycle 1, then Cycle 2, and begin maintenance from Cycle 3 onwards. If repriming is required during the maintenance phase (Cycle 3 onwards), magrolimab dosing frequency and safety assessments should follow Cycle 1 and subsequent dosing should resume maintenance dosing at the next assigned cycle.

Criteria for permanent discontinuation of magrolimab include the following:

- Grade 4 IRR occurring with the first dose (priming dose)
- Grade 4 nonhematologic AE related to magrolimab that does not improve to Grade 2 or baseline within 30 days

If magrolimab is discontinued for reasons other than disease progression, the remaining drug(s) in the combination regimen may be continued.

Treatment delays (not due to AEs) of more than 4 weeks (such as an unrelated medical condition with expected recovery) must be approved by the sponsor.

Table 8. Repriming Guidelines for Magrolimab (Safety Run-in Cohort 1 and Phase 2 Cohort 1)

Dose	Dosing Frequency	Minimum Duration of Treatment Gap[a] That Will Lead to Repriming
1 mg/kg	NA–used at initial priming	2 weeks
15 mg/kg	Weekly (during Cycles 1 and/or 2)	2 weeks
	Every 2 weeks (from Cycle 3)	4 weeks
20 mg/kg	Weekly (during Cycles 1 and/or 2)	2 weeks
	Every 2 weeks (from Cycle 3)	4 weeks
30 mg/kg	Weekly (during Cycles 1 and/or 2)	2 weeks
	Every 2 weeks (from Cycle 3)	4 weeks

NA = not applicable
a Repriming gap starts the day after the last dose of magrolimab and consists of the total consecutive days on which magrolimab is not administered.

Table 9. Repriming Guidelines for Magrolimab (Safety Run-in Cohort 2 and Phase 2 Cohort 2)

Dose	Dosing Frequency	Minimum Duration of Treatment Gap[a] That Will Lead to Repriming
1 mg/kg	NA–used at initial priming	2 weeks
15 mg/kg	Weekly (during Cycles 1 and/or 2)	2 weeks
20 mg/kg	Weekly (during Cycles 1 and/or 2)	2 weeks
30 mg/kg	Weekly (during Cycles 1 and/or 2)	2 weeks
	Every 3 weeks (from Cycle 3)	4 weeks
45 mg/kg	Every 3 weeks (from Cycle 3)	4 weeks
60 mg/kg	Every 3 weeks (from Cycle 3)	4 weeks

NA = not applicable
a Repriming gap starts the day after the last dose of magrolimab and consists of the total consecutive days on which magrolimab is not administered.

If planned surgical procedures are needed for patients on study treatment, magrolimab will be delayed and restarted in accordance with Table 10.

Table 10. Magrolimab Dosing Guidance for Planned Surgical Procedures on Study

Planned Surgical Procedure	Magrolimab Dose Guidance
Minimally invasive procedure (Examples: biopsies [excluding lung/liver], skin/subcutaneous lesion removal, cataract/glaucoma/eye surgery/cystoscopy)	Hold magrolimab dose 3 days prior to procedure and restart after 3 days
Moderately invasive procedure (Examples: lung/liver biopsy, hysterectomy, cholecystectomy, hip/knee replacement, minor laparoscopic procedures, stent/angiopathy)	Hold magrolimab dose 3 days prior to procedure and restart after 5 days
Highly invasive procedure (Examples: central nervous system/spine surgery, major vascular surgery, cardiothoracic surgery, major laparoscopic surgery)	Hold magrolimab dose 3 days prior to procedure and restart after 7 days

5.8. Magrolimab Premedication and Prophylaxis

Premedication is required prior to the administration of the first 2 doses of magrolimab and in case of reintroduction with repriming. Premedication should include oral acetaminophen 650 to 1000 mg, oral or IV diphenhydramine 25 to 50 mg, and IV dexamethasone 4 to 20 mg, or comparable regimen. Premedication decisions during subsequent infusions should be based on the treating physician's clinical judgment and the presence/severity of prior IRRs. Guidance is provided in Section 7.8.1.3, Management of Infusion-Related Reactions.

5.9. Prior and Concomitant Medications

5.9.1. Prior and Concomitant Medications With Magrolimab

5.9.1.1. Permitted Concomitant Medications

Premedication and prophylaxis for AEs is permitted while on study treatment. Palliative and/or supportive medications, such as pain medications, bone-modifying medications (bisphosphonates or denosumab), antiemetics or antidiarrheal medications, and growth factor support are allowed at the investigator's discretion. Palliative, localized non-CNS radiotherapy, is permitted to areas of nontarget disease on study; refer to Section 6.6 for the response assessment details regarding palliative radiotherapy allowed in this study. Corticosteroid use is permitted for symptomatic treatment, premedication, pseudoprogression, and/or specific patient conditions. Chronic high-dose steroid use is not recommended unless clinically indicated. Red blood cell and platelet transfusions are permitted during the study as clinically indicated and should be recorded in the electronic case report form (eCRF) dedicated to on-study transfusions. All 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 30-day Safety Follow-up Visit should be recorded in the eCRF. Only the drug name, indication, route, and dates of concomitant medications will be captured in the eCRF.

5.9.1.2. Coronavirus Disease 2019 (COVID-19) Vaccine

There is no contraindication to the COVID-19 vaccine with magrolimab. There is no specific recommendation on the timing of a COVID-19 vaccine; individuals may receive the vaccine when available. However, if these patients are neutropenic, investigators may use local guidance as well as clinical judgment in determining the timing of the COVID-19 vaccine. Investigators should document vaccinations. Investigators should notify patients of the risks of delaying the COVID-19 vaccination and document this along with any mitigation strategies for preventing COVID-19 infection. See Appendix 3 for the Pandemic Risk Assessment and Mitigation Plan.

5.9.1.3. Prohibited Concomitant Medications

Anticancer therapies including chemotherapy, targeted therapies, and immunotherapy (apart from study drugs) are not permitted while patients are on study.

5.9.2. Prior and Concomitant Medications With Nab-paclitaxel and Paclitaxel

The current local prescribing information should be followed for permitted and prohibited concomitant medications of nab-paclitaxel and paclitaxel.

5.9.3. Prior and Concomitant Medications With Sacituzumab Govitecan

Palliative and/or supportive medications, such as pain medications, bone-modifying medications (bisphosphonates or denosumab), antiemetics or antidiarrheal medications, transfusions, and growth factor support are allowed at the investigator's discretion. Palliative radiotherapy is permitted.

5.9.3.1. Prior and Concomitant Medications That Are Prohibited or Used With Caution With Sacituzumab Govitecan

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

- Systemic anticancer therapies, aside from the study drugs. High-dose systemic corticosteroids (≥ 20 mg of prednisone or its equivalent) are not allowed within 2 weeks of Cycle 1 Day 1. It should be noted that premedication with corticosteroids or the use of corticosteroids for treatment-related AEs are permitted.
- Live vaccines (examples include, but are not limited to, intranasal influenza vaccines, typhoid [oral] vaccines, and Bacillus Calmette-Guerin vaccine) within 30 days prior to randomization and while receiving study treatment.

Caution should be used when the following medications are used while the patient is receiving study treatment:

- UGT1A1 Inhibitors
  - SN-38 (the active metabolite of sacituzumab govitecan) is metabolized via human UGT1A1. Coadministration of sacituzumab govitecan with inhibitors of UGT1A1 may increase systemic exposure to the active metabolite, SN-38. UGT1A1 inhibitors should not be administered concomitantly with sacituzumab govitecan unless there are no therapeutic alternatives. A list of example UGT1A1 inhibitors is provided in Appendix 11.
- UGT1A1 Inducers
  - SN-38 (the active metabolite of sacituzumab govitecan) is metabolized via human UGT1A1. Exposure to SN- 38 may be substantially reduced in patients concomitantly receiving UGT1A1 enzyme inducers. UGT1A1 inducers should not be administered concomitantly with sacituzumab govitecan unless there are no therapeutic alternatives. A list of example UGT1A1 inducers is provided in Appendix 11.
- COVID-19 Vaccines
  - There is no substantial safety or efficacy data regarding the concurrent administration of the coronavirus disease 2019 (COVID-19) vaccine and sacituzumab govitecan. Patients are allowed to receive COVID-19 vaccines to reduce the risk and complications of COVID-19 infection, provided they are not live-attenuated vaccines. The study visits should continue as planned if vaccination occurs while the patient is on the study. See Appendix 3 for the Pandemic Risk Assessment and Mitigation Plan.

Should patients have a need to initiate treatment with any prohibited concomitant medication, the Gilead medical monitor must be consulted, and approval granted before initiation of the new medication. In instances where a prohibited medication is initiated before discussion with the Gilead medical monitor, the investigator must notify Gilead as soon as he/she is aware of the use of the prohibited medication.

5.10. Dosage and Administration of Nab-paclitaxel and Paclitaxel

Nab-paclitaxel and paclitaxel should be administered according to local guidelines and practices. Study-specific considerations for nab-paclitaxel or paclitaxel dosing regimens for Safety Run-in Cohort 1 and Phase 2 Cohort 1 are described in Table 4 and Table 5, respectively.

For patients receiving magrolimab in combination with paclitaxel/nab-paclitaxel, Cycle 1 Day 1 treatment can be administered over 2 days such that magrolimab is administered on Cycle 1 Day 1 and paclitaxel/nab-paclitaxel on Cycle 1 Day 2. This also applies to repriming cycles that require Cycle 1 Day 1 dosing of magrolimab. Cycle 1 Day 1 dosing and infusion time requirements for each agent should be followed, as listed in Table 4 and Table 5. Premedication guidelines should be followed prior to magrolimab (see Section 5.8), paclitaxel/nab-paclitaxel (see Section 5.11). Patients should be observed during and following the infusion for signs or symptoms of IRRs (see Section 5.6 for magrolimab).

5.11. Nab-paclitaxel and Paclitaxel Premedication and Prophylaxis

Nab-paclitaxel and paclitaxel should be administered according to local guidelines and practices.

Premedication for nab-paclitaxel is not required for prophylaxis. In contrast to paclitaxel (see below), steroid premedication is not required for use with nab-paclitaxel. However, patients with hypersensitivity reaction or IRR to nab-paclitaxel may be premedicated with corticosteroids for future dose administration at the discretion of the treating physician and can be discontinued for subsequent treatments if clinically indicated.

All patients should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions per their institutional standard of care or as follows. Such premedication may consist of oral dexamethasone 10 mg to 20 mg administered approximately 12 and 6 hours before paclitaxel or dexamethasone less than or equal to 10 mg IV within 1 hour prior to paclitaxel infusion, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg IV) or its equivalent IV 30 to 60 minutes before paclitaxel.

If paclitaxel is well tolerated during the first 2 weekly doses without an apparent hypersensitivity reaction, a taper in the dose of dexamethasone premedication (or equivalent) may be considered for subsequent cycles if permitted by institutional standard of care. This approach has been reported to be successful in the literature {Berger 2012}.

5.12. Dose Modifications for Nab-paclitaxel and Paclitaxel

Nab-paclitaxel and paclitaxel should be administered according to local guidelines and practices. Study-specific considerations for nab-paclitaxel or paclitaxel are provided as follows:

5.12.1. Hematologic Toxicity

Nab-paclitaxel and paclitaxel are known to cause myelosuppression. The ANC must be at least 1500 cells/µL and platelet count must be at least 100,000 cells/µL on Day 1 of each cycle. Nab-paclitaxel and paclitaxel should not be administered on Days 8 or 15 of the cycle until counts recover to an ANC at least 500 cells/µL and platelets at least 50,000 cells/µL.
If nab-paclitaxel or paclitaxel cannot be administered on Day 15 of the cycle, the next dose of nab-paclitaxel or paclitaxel should be administered on Day 1 of the following cycle when ANC and platelet counts have recovered to permissible levels. When dosing resumes, the nab-paclitaxel or paclitaxel doses should be permanently reduced as outline in Table 11.

Table 11. Nab-paclitaxel and Paclitaxel Reductions for Hematologic Toxicity

Hematologic Toxicity	Occurrence	Weekly Nab-paclitaxel Dose (mg/m^2)	Weekly Paclitaxel Dose (mg/m^2)
Neutropenic fever (nadir ANC < 500 cells/µL with fever > 38 °C) or Delay of next cycle by > 7 days for nadir ANC < 1500 cells/µL or Nadir ANC < 500 cells/µL for > 7 days	First	80	72
	Second	60	54
	Third	Discontinue treatment	Discontinue treatment
Nadir platelet count < 50,000 cells/µL	First	80	72
	Second	Discontinue treatment	Discontinue treatment

ANC = absolute neutrophil count

5.12.2. Neurological Toxicity

Table 12 presents the nab-paclitaxel and paclitaxel dose reductions for neurological toxicity. Nab-paclitaxel or paclitaxel should be withheld for Grade 3 or 4 peripheral neuropathy and may be resumed at reduced doses when peripheral neuropathy recovers to Grade 1 or full resolution.

Table 12. Nab-paclitaxel and Paclitaxel Dose Reductions for Neurological Toxicity

Neurological Toxicity	Occurrence	Weekly Nab-paclitaxel Dose (mg/m^2)	Weekly Paclitaxel Dose (mg/m^2)
Grade 3 or 4 peripheral neuropathy	First	Withhold treatment until resolves to ≤ Grade 1, then resume treatment at 80 mg/m^2	Withhold treatment until resolves to ≤ Grade 1, then resume treatment at 72 mg/m^2
	Second	Withhold treatment until resolves to ≤ Grade 1, then resume treatment at 60 mg/m^2	Withhold treatment until resolves to ≤ Grade 1, then resume treatment at 54 mg/m^2
	Third	Discontinue treatment	Discontinue treatment

5.12.3. Hepatic Toxicity

Nab-paclitaxel should be withheld for Grade 3 or 4 hepatic toxicity as specified in Table 13. Given that magrolimab can cause a transient increase in indirect bilirubin due to on-target anemia, dose modifications for nab-paclitaxel in the case of bilirubin must not be attributed to magrolimab. In addition, the investigator should make all efforts to exclude malignant disease progression as a cause of liver enzyme derangement, which would not be considered a toxicity for nab-paclitaxel.

Table 13. Nab-paclitaxel and Paclitaxel Dose Reductions for Hepatic Toxicity

Hepatic Toxicity	Nab-paclitaxel Dose Modification	Paclitaxel Dose Modification
AST level < 10 × ULN **or** Bilirubin level < ULN to 1.25 × ULN (not attributed to magrolimab and is mostly direct)	No dose modification; proceed with 100 mg/m^2	No dose modification; proceed with 90 mg/m^2
AST level < 10 × ULN **and** Bilirubin level > 1.25 to 2 × ULN (not attributed to magrolimab and is mostly direct)	Interrupt treatment until AST level < 10 × ULN **and** bilirubin ≤ 1.25 × ULN, then reduce to 80 mg/m^2. If toxicity does not resolve to above criteria within 3 weeks, discontinue treatment.	Interrupt treatment until AST level < 10 × ULN **and** bilirubin ≤ 1.25 × ULN, then reduce to 72 mg/m^2. If toxicity does not resolve to above criteria within 3 weeks, discontinue treatment.
AST level < 10 × ULN **or** Bilirubin level > 2.00 to 5 × ULN (not attributed to magrolimab and is mostly direct)	Interrupt treatment until AST level < 10 × ULN **and** bilirubin ≤ 1.25 × ULN, then reduce to 60 mg/m^2. If toxicity does not resolve to above criteria within 3 weeks, discontinue treatment.	Interrupt treatment until AST level < 10 × ULN **and** bilirubin ≤ 1.25 × ULN, then reduce to 54 mg/m^2. If toxicity does not resolve to above criteria within 3 weeks, discontinue treatment.
AST level > 10 × ULN **or** Bilirubin level > 5 × ULN (not attributed to magrolimab and is mostly direct)	Discontinue treatment	Discontinue treatment

AST = aspartate aminotransferase; ULN = upper limit of normal

5.12.4. Pneumonitis

Interstitial pneumonitis has been observed in less than 1% of patients with nab-paclitaxel monotherapy and 4% with use of nab-paclitaxel in combination with gemcitabine. Monitor patients closely for signs and symptoms of pneumonitis.

Nab-paclitaxel should be permanently discontinued upon ruling out infectious etiology and making a diagnosis of pneumonitis related to nab-paclitaxel. Promptly initiate appropriate treatment and supportive measures. After ruling out infectious etiology, IV corticosteroid therapy should be instituted without delay, with appropriate premedication and secondary pathogen coverage. Treatment per institutional guidelines may be used.

5.12.5. Other Toxicities

For any Grade 3 or 4 toxicity not mentioned above, related to nab-paclitaxel or paclitaxel, nab-paclitaxel or paclitaxel should be held until the patient recovers to Grade 1 or lower or baseline. Nab-paclitaxel or paclitaxel may be resumed at reduced doses when toxicity recovers to Grade 1 or lower or baseline. The treatment should then be resumed at 75% dose (permanent dose reduction) (Table 14). If recovery to Grade 1 or lower or baseline does not

occur within 3 weeks, then nab-paclitaxel or paclitaxel should be discontinued. No dose reductions should be made for Grade 1 or 2 toxicities.

Table 14. Nab-paclitaxel and Paclitaxel Dose Reductions for Nonhematologic, Nongastrointestinal, Nonneurologic, and Nonhepatic Toxicity, Nonpneumonitis Toxicity

Adverse reaction	Occurrence	Weekly Nab-paclitaxel Dose (mg/m^2)	Weekly Paclitaxel Dose (mg/m^2)
Grade 3 or 4 nonhematologic, nongastrointestinal, nonneurologic, nonhepatic toxicity	First	80	72
	Second	60	54
	Third	Discontinue treatment	Discontinue treatment

5.13. Dosage and Administration of Sacituzumab Govitecan

5.13.1. Sacituzumab Govitecan

Please use Pharmacy Manual as primary source of instructions for study drug preparation.

- Administer sacituzumab govitecan at 10 mg/kg as an IV infusion on Days 1 and 8 of a 21-day cycle. Sacituzumab govitecan should not be administered as an IV push or bolus.
- The dose of sacituzumab govitecan will be calculated based on actual weight at enrollment/randomization (using weight obtained either at screening or on Cycle 1 Day 1) and should remain constant throughout the study, unless there is a greater than 10% change in body weight from baseline. Modifications to the study treatment doses administered should be made for a greater than 10% change in body weight from baseline and according to local and regional prescribing standards. Dose modifications for changes in body weight less than 10% may be made according to local institutional guidelines.
- Administer the first infusion over 3 hours. Subsequent infusions may be administered over 1 to 2 hours if previous infusions were well tolerated. Monitor the patient during, and for at least 30 minutes after infusion.
- Protect the infusion bag from light.
- An infusion pump may be used.
- Compatibility with polypropylene, polyvinyl chloride, polypropylene and ethylene/propylene copolymer infusion bags has been demonstrated and are acceptable for use with sacituzumab govitecan.
- Do not mix sacituzumab govitecan, or administer as an infusion, with other medicinal products.

- Upon completion of the infusion, flush the IV line with 20 mL 0.9% sodium chloride injection.

- Sacituzumab govitecan is a cytotoxic drug and applicable special handling and disposal procedures should be followed.

For patients receiving magrolimab in combination with sacituzumab govitecan (Safety Run-in Cohort 2 and Cohort 2), Cycle 1 Day 1 treatment can be administered over 2 days such that magrolimab is administered on Cycle 1 Day 1 and sacituzumab govitecan on Cycle 1 Day 2. This also applies to repriming cycles that require Cycle 1 Day 1 dosing of magrolimab. Cycle 1 Day 1 dosing and infusion time requirements for each agent should be followed, as listed in Table 6 and Table 7. Premedication guidelines should be followed prior to magrolimab (see Section 5.8) and sacituzumab govitecan (see Section 5.14). Patients should be observed during and following the infusion for signs or symptoms of IRRs (see Section 5.6 for magrolimab and Section 5.13 for sacituzumab govitecan).

5.14. Sacituzumab Govitecan Premedication and Prophylaxis

Guidance for premedication for prevention of toxicities associated with sacituzumab govitecan is presented in Table 15.

Table 15. Guidance for Premedication and Prophylaxis for Toxicities Associated With Sacituzumab Govitecan

Potential Reaction	Premedication and Prophylaxis Guidance
Infusion-related reaction	• Antipyretics and H1/H2 blockers should be administered before each sacituzumab govitecan infusion. • Corticosteroids (hydrocortisone 50 mg or equivalent PO or IV) may be administered prior to infusions.
Nausea and vomiting	• Premedication with a 2-drug antiemetic regimen is recommended. • If nausea and vomiting are persistent, a 3-drug regimen may be used, including a 5-HT3 inhibitor (ondansetron or palonosetron, or other agents according to local practices), an NK1-receptor antagonist (fosaprepitant or aprepitant), and dexamethasone (10 mg PO or IV). • Anticipatory nausea can be treated with olanzapine.
Neutropenia	• Complete blood counts must be obtained prior to each sacituzumab govitecan infusion and treatment should be administered if ANC meets the following criteria: – Day 1: ANC $\geq 1500/mm^3$ – Day 8: ANC $\geq 1000/mm^3$ • Use of G-CSF: Primary prophylaxis is highly recommended for patients at risk of febrile neutropenia based on current ASCO/ESMO guidelines for use of growth factors. Secondary prophylaxis for ≥ 3 Grade neutropenia is recommended.

ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology, G-CSF = granulocyte-colony stimulating factor; IV = intravenous; PO = orally

5.15. Dose Modifications for Sacituzumab Govitecan

The major toxicities of sacituzumab govitecan are expected to be gastrointestinal symptoms and neutropenia. Premedication and prophylaxis for the prevention of sacituzumab govitecan-associated toxicities are described in Section 5.14. Management of toxicities should be in accordance with best clinical practices, standard institutional guidelines, and current ASCO/ESMO guidelines. All patients will be closely monitored over the course of their treatment and aggressively medically managed, including dose reduction and interruption, to prevent the need for treatment discontinuation and serious complications of these toxicities.

All efforts to avoid dose reduction should be taken to address toxicity prior to initiation of dose reduction. Use of primary and secondary prophylaxis with granulocyte-colony stimulating factor (G-CSF) is highly recommended for patients at risk for high grade neutropenia and febrile neutropenia. Instructions for dose modification and discontinuation of sacituzumab govitecan for treatment-related toxicities are provided in Section 5.15.2 and instructions for treatment delays are provided in Section 5.15.1. Instructions for management of toxicities known to occur with sacituzumab govitecan is provided in Section 7.8.3.

Treatment delays for other study drugs are described in Section 5.6.1 (magrolimab) and Section 5.12 (nab-paclitaxel and paclitaxel). Dose modification and discontinuations are described in Section 5.7 (magrolimab) and Section 5.12 (nab-paclitaxel and paclitaxel).

5.15.1. Treatment Delays for Sacituzumab Govitecan

Sacituzumab govitecan will be administered in 21-day cycles on Days 1 and 8; the next cycle should start 14 days after the Day 8 dose (ie, the Day 8 infusion will be counted as the first day of that 14-day period). However, visit windows of ± 3 days of the scheduled infusion are permitted. At a minimum, 6 days are required between sacituzumab govitecan doses. The scheduled Day 1 and Day 8 infusions may be delayed for up to 3 weeks for treatment-related toxicities.

Instructions for dose delays and dose reductions for specific toxicities are summarized below. See Table 15 for when sacituzumab govitecan can be administered based on ANC. Withhold sacituzumab govitecan administration for Grade 3 nausea or Grade 3 or 4 diarrhea or vomiting at the time of the scheduled treatment administration and resume sacituzumab govitecan when resolved to at least Grade 1. For toxicities not specifically addressed in Table 16, dosing may be delayed for greater than Grade 2 toxicities related to sacituzumab govitecan treatment for a maximum of 3 weeks. If the toxicity has improved to at least Grade 2, the dose should be administered at that time. For a toxicity that delays Day 8 dosing, if treatment is delayed for more than 1 week, dosing should resume as Day 1 of the next cycle. Regardless of whether the Day 8 dose is delayed for toxicity, there should be 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

Palliative radiotherapy is permitted. If there is clear evidence of clinical benefit, treatment may be continued after completion of palliative radiotherapy. In this case, sacituzumab govitecan administration should be interrupted 1 week before the procedure and reinstated no earlier than 2 weeks after the procedure. In the event a patient requires surgery, sacituzumab govitecan should be interrupted 1 week before the procedure if clinically feasible and dosing should be held for 2 weeks after the procedure. Dosing may resume thereafter if the patient is clinically stable. Extensive surgical procedures (eg, abdominal, cranial surgeries) may require suspension of dosing for 4 weeks to allow for an adequate period for healing before dosing may resume. The study medical monitor must approve continuation of therapy with sacituzumab govitecan before resumption of dosing (see Section 3.4 for discontinuation criteria).

Treatment interruptions for reasons other than resolution of toxicities/procedures are not permitted outside of the permitted visit windows.

5.15.2. Dose Reductions and Discontinuation for Sacituzumab Govitecan

Table 16 summarizes recommendations for sacituzumab govitecan dose reductions and discontinuations for treatment-related toxicities.

Sacituzumab govitecan dose reductions and interruptions will be managed based on toxicity severity. Leukopenia or lymphopenia in the absence of neutropenia does not require dose modification. The sacituzumab govitecan dose must not be re-escalated following a dose reduction.

The sacituzumab govitecan treatment must be discontinued if there is more than a 5-week dose delay from the planned treatment date, regardless of reason, or more than a 3-week dose delay from the planned treatment date due to sacituzumab govitecan-related toxicity.

Table 16. Recommended Dose Modification Schedule for Sacituzumab Govitecan

Adverse Reaction	Occurrence	Dose Modification or Action
Severe neutropenia		
Grade 4 neutropenia ≥ 7 days, OR Grade 3-4 febrile neutropenia, OR At time of scheduled treatment, Grade 3 or 4 neutropenia that delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1	First	25% dose reduction from initial dose and administer G-CSF as soon as clinically indicated. Initiate secondary prophylaxis with G-CSF.
	Second	50% dose reduction from initial dose and administer G-CSF as soon as clinically indicated. Initiate secondary prophylaxis with G-CSF, if not done earlier.
	Third	Discontinue Treatment
At time of scheduled treatment, Grade 3 or 4 neutropenia that delays dosing beyond 3 weeks for recovery to ≤ Grade 1	First	Discontinue treatment
Severe nonneutropenic toxicity		
Grade 4 nonhematologic toxicity of any duration, OR Any Grade 3 or 4 nausea, vomiting, or diarrhea due to treatment that is not controlled with antiemetics and antidiarrheal agents, OR Other Grade 3 or 4 nonhematologic toxicity persisting > 48 hours despite optimal medical management, OR At time of scheduled treatment, Grade 3 or 4 nonneutropenic hematologic or nonhematologic toxicity that delays dose by 2 or 3 weeks for recovery to ≤ Grade 1	First	25% dose reduction
	Second	50% dose reduction
	Third	Discontinue treatment
In the event of Grade 3 or 4 nonneutropenic hematologic or nonhematologic toxicity that does not recover to ≤ Grade 1 within 3 weeks	First	Discontinue treatment
Infusion-Related Toxicities		
Grade 2 or Grade 3 infusion-related reaction despite optimal management	Recurrent	Discontinue treatment
Grade 4 infusion-related reaction	First	Discontinue treatment

G-CSF = granulocyte-colony stimulating factor

5.16. Accountability for Investigational Medicinal Product

The investigator is responsible for ensuring adequate accountability of all used and unused study drug (kits, vials, etc). 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 (kits, vials, etc)
- The date, patient number, and the study lot number dispensed
- The date, quantity of used and unused study drug returned, along with the initials of the person recording the information

5.16.1. 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 the electronic trial 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.

6. STUDY PROCEDURES

The study procedures to be conducted for each patient enrolled in the study are presented in tabular form in Appendix Table 1, Appendix Table 2, and Appendix Table 3, and described in the following sections.

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

6.1. Patient Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment onto the study. 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.

Treatment assignment for patients in Phase 2 Cohort 1 will be randomized using IRT. Patients will be assigned to receive magrolimab in combination with choice of either nab-paclitaxel or paclitaxel or either nab-paclitaxel or paclitaxel in a 1:1 ratio. Nab-paclitaxel or paclitaxel use will be per investigator discretion and in accordance with local guidelines and practices.

Patients in Phase 2 Cohort 2 will be assigned to receive magrolimab in combination with sacituzumab govitecan.

6.2. Pretreatment Assessments

6.2.1. Prescreening

Prior to providing consent for the study, an optional prescreening consent form may be offered to patients at the investigator's discretion to permit the collection and analysis of blood samples for extended RBC phenotyping or genotyping, type and screen (ABO/Rh [any of the 4 blood groups A, B, AB, and O comprising the ABO system/Rhesus factor]), and direct antiglobulin test (DAT).

6.2.2. Screening Visit

Patients will be screened within 30 days before dosing on Cycle 1 Day 1 to determine eligibility for participation in the study. Assessments performed as part of standard of care prior to ICF signature may be used if they are within the required screening period. For patients enrolled in Cohort 1 Arm B with documented progressive disease that rescreen to enroll in Cohort 2, assessments performed under Cohort 1 patient ID can be used if within the required screening period. The following will be performed and documented at screening per Appendix 2:

- Obtain written informed consent
- Obtain medical history including concomitant medications
- Obtain demographic information

- Complete physical examination, including vital signs, body weight, and height
- Confirm diagnosis of TNBC by histology or cytology performed at a local laboratory
- Obtain PD-L1 test result (if prior diagnostic PD-L1 report is not available)
- Obtain blood and urine samples for the following tests: chemistry, hematology, coagulation, urinalysis, serum pregnancy, blood phenotyping or genotyping, type and screen, and DAT (Section 6.4.2). Blood for biomarker samples will also be collected
- Tumor biopsy (Section 6.9)
- ECOG
- Perform 12-lead ECG (single)
- Record all serious AEs (SAEs) related to protocol-required procedures occurring after signing of the ICF

From the time of obtaining informed consent through the first administration of study drug, record all SAEs that are considered related to protocol-mandated procedures on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be considered medical history. For patients enrolled in Cohort 1 Arm B with documented progressive disease that rescreen to enroll in Cohort 2, AEs should be reported under their Cohort 1 patient ID until they receive the first treatment dose in Cohort 2, and ongoing AEs from Cohort 1 should be captured as medical history. See Section 7, Adverse Events and Toxicity Management, for additional details.

6.3. Randomization

Randomization procedures are described in Section 5.1.1. Randomization for Phase 2 Cohort 1 must be conducted within 3 days of dosing on Cycle 1 Day 1.

6.4. Treatment Assessments

6.4.1. Pregnancy Test

Pregnancy tests are required only for female patients of childbearing potential. Note that a woman is considered to be of childbearing potential following the initiation of puberty (Tanner Stage 2) until becoming postmenopausal, unless permanently sterile or with medically documented ovarian failure. Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female patient of any age. Women are considered to be in a postmenopausal state when they are at least 54 years of age with cessation of previously occurring menses for at least 12 months without an alternative cause. In addition, women of less than 54 years of age with amenorrhea of at least 12 months may also be considered postmenopausal if their follicle-stimulating hormone level is in the postmenopausal

range and they are not using hormonal contraception or hormonal replacement therapy. A negative serum pregnancy test is required at screening, and a negative pregnancy test is required prior to study treatment administration on Cycle 1 Day 1. The Cycle 1 Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was performed within the 72 hours before study treatment administration. Pregnancy tests will also be required at Day 1 of each subsequent cycle and continue monthly up to 6 months after the end of treatment (EOT) per the duration of required contraception as discussed in Appendix 5. For further details, refer to Appendix 5.

6.4.2. Type and Screen and Direct Antiglobulin Test

Due to the risk of developing anemia, blood type and screen (ABO/Rh), DAT, and extended RBC phenotyping (including minor antigens such as Rh, CcDEe, Cw, MNSs, Kk, Fya, Fyb, Jka, and Jkb) will be performed at screening before exposure to magrolimab, as described in Section 7.8.1.1. An extended genotype (instead of an RBC phenotype) will be performed if a patient received any RBC or whole blood transfusion within the previous 3 months. Extended RBC genotyping instead of extended RBC phenotyping is acceptable for any patient. Red blood cell phenotyping/genotyping, ABO type, and DAT need not be repeated if results dated before screening are available. Antibody screen need not be repeated if results dated before screening are available, unless the patient was transfused since that time. Results must be available before the first dose of magrolimab.

6.4.3. Vital Signs

Vital signs are to include heart rate, respiratory rate, oxygen saturation, blood pressure, temperature, and weight. Height will be recorded during screening only. Weight will be recorded during screening and on Day 1 of each cycle. Vital signs are to be recorded prior to infusion/injection of magrolimab, nab-paclitaxel, paclitaxel, or sacituzumab govitecan at the visits specified in the schedules of assessments in Appendix Table 1, Appendix Table 2, and Appendix Table 3.

6.4.4. Physical Examination

Complete physical examination is to be performed at screening. Thereafter, symptom-directed physical examinations are acceptable and may also include routine examination of the skin (including fingers, toes, and ears) and neurologic system.

6.4.5. Performance Status

Performance status will be scored using the ECOG performance status scale index (refer to Appendix 8).

6.4.6. Electrocardiograms

A single ECG will be performed at screening. Additional ECG requirements for sites in the UK are provided in Appendix 12.

6.4.7. Patient-reported Outcomes

Three PRO instruments will be administered in Phase 2 Cohort 1 of this study: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire (EORTC-QLQ-C30) and accompanying breast cancer module (EORTC-QLQ-BR23) and the EQ-5D-5L. The patient should complete these questionnaires before any other study procedures conducted the same day at required visits. Please refer to schedules of assessments in Appendix Table 1 and Appendix Table 3 for timing of PRO assessments. If the PRO questionnaires are unavailable in a patient's language, completion is not required. Patients with other barriers to questionnaire completion may be exempt from these assessments after discussion with the sponsor.

6.4.7.1. EORTC-QLQ-C30 and EORTC-QLQ-BR23

The EORTC-QLQ-C30 is a reliable and valid measure of PRO and has been widely used among cancer patients. The EORTC-QLQ-C30 includes 30 separate questions (items) resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain) and 6 single items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties) {Fayers 2001}. The recall period is 1 week (past week). It will take about 11 minutes to complete. The accompanying module for breast cancer, EORTC-QLQ-BR23, has an additional 23 questions.

6.4.7.2. EQ-5D-5L

The EQ-5D-5L is an instrument for use as a measure of health outcome {EuroQol Research Foundation 2017, Janssen 2013}. The EQ-5D-5L consists of 2 sections: the EuroQol (5 dimensions) (EQ-5D) descriptive system and the EQ visual analogue scale (EQ-VAS). A sample is provided in Appendix 7.

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the patient's health state.

The EQ-VAS records the patient's self-rated health on a vertical VAS, where the endpoints are labeled "the best health you can imagine" and "the worst health you can imagine." The EQ-VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgment.

6.4.8. Adverse Events

At each visit, all AEs observed by the investigator or reported by the patient that occur after the first dose of study treatment through 30 days after the last dose of study treatment are to be reported using the applicable eCRF (Section 7.1.1). Full details on the definitions, assessment and reporting instructions for AEs are provided in Section 7.

6.4.9. Concomitant Medications

All concomitant medications taken by the patient while on study are to be documented. Changes in baseline concomitant medication information is to be collected after informed consent through the study treatment period, and up until 30 days after treatment discontinuation. Concomitant medication associated with procedure-related AEs will be captured from the time of informed consent and onward. Information to be collected includes therapy name, indication, route, start date, and stop date and must be reported using the applicable eCRF. Note that any anticancer therapies after the study treatment period should also be collected per the schedules of assessments (Appendix Table 3).

6.5. Safety Assessments

Table 17 presents analytes to be assessed by the local and/or central laboratory or specialty laboratories at screening. Refer to Section 7.8.1.2 for hemoglobin testing requirements for the first 2 magrolimab doses predose and postdose monitoring.

Table 17. Screening Laboratory Analytes

Chemistry (Serum or Plasma)	Hematology	Urinalysis[a]	Other Laboratory Measurements
Sodium Potassium Chloride Bicarbonate[b] Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or urea Creatinine Uric acid Total bilirubin Direct bilirubin Indirect bilirubin AST (SGOT) ALT (SGPT) Alkaline phosphatase	RBC Hemoglobin Hematocrit Platelets WBC Absolute neutrophil count Eosinophils Basophils Lymphocytes Monocytes Reticulocytes **Coagulation** PT INR aPTT or PTT	Glucose Protein Urine pH Ketones Bilirubin Urine specific gravity	Pregnancy (serum) Blood phenotyping or genotyping[c] Type and screen (ABO/Rh), DAT

ABO = any of the 4 blood groups A, B, AB, and O comprising the ABO system; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DAT = direct antiglobulin test; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; Rh = Rhesus factor; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell

a Reflex microscopic testing based on other abnormalities.

b If available at local laboratory.

c Test may be performed at a central laboratory or local laboratory, if available.

Analytes are required to be collected at or before screening. Refer to Appendix Table 1 and Appendix Table 2 for collection time points.

Table 18 presents analytes to be assessed by the local and/or central laboratory or specialty laboratories during the study.

Table 18. Study Laboratory Analytes

Chemistry (Serum or Plasma)	Hematology	Other Laboratory Measurements
Sodium Potassium Chloride Bicarbonate[a] Total protein Albumin Calcium Magnesium Phosphorus (serum) Glucose BUN or urea Creatinine Uric acid (serum) Total bilirubin Direct bilirubin Indirect bilirubin AST (SGOT) ALT (SGPT) Alkaline phosphatase Haptoglobin LDH	RBC Hemoglobin Hematocrit Platelets WBC Absolute neutrophil count Eosinophils Basophils Lymphocytes Monocytes Reticulocytes	Pregnancy (urine or serum) Blood and tumor samples for biomarker analysis Pharmacokinetics[b] Antidrug antibodies[b]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; LDH = lactate dehydrogenase; RBC = red blood cell; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell

a If available at local laboratory.

b These assays will be performed at a central laboratory.

Analytes are required to be collected at visits during study. Refer to Appendix Table 1, Appendix Table 2, and Appendix Table 3 and for collection time points.

6.6. Efficacy Assessments

For the Safety Run-in Cohort 1 and Phase 2 Cohort 1, computed tomography (CT) or magnetic resonance imaging (MRI) scans with IV contrast of the chest, abdomen, pelvis, and other involved disease sites are to be performed at the screening visit, every 8 weeks (± 7 days) during the study (starting from Cycle 1 Day 1), and at the EOT visit if one has not been performed within the last 30 days or progressive disease has been documented.

For Safety Run-in Cohort 2 and Phase 2 Cohort 2, CT or MRI scans with IV contrast of the chest, abdomen, pelvis, and other involved disease sites are to be performed at the screening visit, every 6 weeks (± 7 days) through 36 weeks (Weeks 6, 12, 18, 24, 30, and 36) during the study, then every 9 weeks (± 7 days) (starting at Cycle 1 Day 1), and at the EOT visit if one has not been performed within the last 30 days or progressive disease has been documented.

A brain MRI with contrast is required for all patients during screening. Patients with a history of or presence of brain metastases at baseline will also be required to have a contrast MRI of the brain performed at the same frequency and schedule as the non-CNS imaging while on treatment. Brain CT will be acceptable if MRI is medically contraindicated.

Tumor burden will be evaluated solely based on radiographic imaging per RECIST, Version 1.1. Chest x-ray, ultrasound, endoscopy, laparoscopy, positron emission tomography (PET), radionuclide scans, or tumor markers will not be considered for response assessment. PET/CT may be utilized per the investigator's discretion if a high-quality CT scan is included.

For radiographic evaluations, the same method of assessment and the same technique (eg, scan type, scanner, patient position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline and during study treatment and follow-up. All sites of measurable and nonmeasurable disease must be documented at screening and reassessed at each subsequent tumor evaluation.

Scans taken as part of standard medical practice up to 30 days prior to enrollment can be used for screening as long as they meet all study requirements. Tumor assessments are to be performed at the time points specified in Appendix Table 1 and Appendix Table 2, regardless of dosing delays or interruptions. Additional scans may be performed at the discretion of the treating physician to assess disease status as clinically indicated.

For patients who stop study treatment in the absence of disease progression per RECIST, Version 1.1 (eg, experience unexpected toxicity), scans should continue to be collected approximately every 8 weeks (± 7 days) for Safety Run-in Cohort 1 and Phase 2 Cohort 1 patients and every 9 weeks (± 7 days) for Safety Run-in Cohort 2 and Phase 2 Cohort 2 patients until disease progression or initiation of systemic antitumor therapy other than the study treatment, whichever is earlier.

All relevant clinical and radiographic information required to make each assessment must be made available for source verification. Disease progression will be determined by the investigator or qualified designee.

Patients will be assessed for response using RECIST, Version 1.1 for the primary efficacy endpoint and for the secondary efficacy endpoint (Appendix 10). Palliative radiation of the target lesion will render that target lesion and subsequent tumor assessments "not evaluable" and should be avoided. Consult with the sponsor prior to palliative radiation if possible. If palliative radiotherapy is given (Section 5.9), presence of new or worsening metastases will be considered progression. If the radiologic assessment does not confirm disease progression, patients should continue to be assessed per the study procedures (Appendix Table 1 and Appendix Table 2).

6.7. Pharmacokinetic Assessments

Magrolimab serum concentration will be measured by a validated enzyme-linked immunosorbent assay (ELISA) immunoassay method.

Blood samples for PK assessment will be collected predose at multiple time points from patients who received magrolimab according to the schedule of assessments in Appendix Table 4. (Note the additional sample collected postdose on Cycle 3 Day 1 at 1 h [± 15 min] after the end of magrolimab infusion.) CCI

[redacted]

6.8. Immunogenicity (Antidrug Antibodies)

Peripheral blood for immunogenicity assessments for ADA against magrolimab will be collected as described in the schedules of assessments for all patients (Appendix Table 4). When collected on the day of study drug dosing, the ADA blood sample must be collected at the same time as the predose PK sample. The presence of anti-magrolimab antibodies will be determined by a validated electrochemiluminescence immunoassay method.

6.9. Biomarker Assessments

Biomarker samples will be collected to assess the PD, MOA, and treatment response biomarkers, and to define correlates of clinical efficacy and/or safety, as outlined in Section 3.8. The biomarker sample collection schedules are outlined in Appendix Table 4.

Patients are required to submit a mandatory pretreatment core needle or excisional tumor biopsy (fine needle aspirate is not adequate) from a site not previously irradiated, unless not feasible as determined by the investigator and discussed with the sponsor. A newly obtained biopsy, collected within 90 days prior to study treatment start, is strongly preferred, but an archival sample is acceptable. For archival samples submitted in lieu of newly obtained biopsies, tissue collected within 6 months prior to study treatment start is strongly preferred whenever possible. Archival samples are requested to be submitted as tissue blocks or, if a block is not available, at least 20 to 25 newly sectioned unstained slides.

Patients will also submit a mandatory on-treatment core needle or excisional tumor biopsy unless not feasible as determined by the investigator and discussed with the sponsor.

For patients enrolled in Cohort 1 Arm B with documented progressive disease that rescreen to enroll in Cohort 2, a tumor biopsy should be performed at the time of rescreening, whenever possible. Alternatively, tissue from on-treatment biopsy submitted as part of Cohort 1 assessments are acceptable, if available. If collection of recent or new tissue is not feasible, the patient may be exempt from the screening tissue requirement with sponsor approval.

For additional details and instructions regarding tissue requirements and procedures for sample collection, storage, and shipment, refer to the Study Laboratory Manual.

6.10. Posttreatment Assessments

Posttreatment assessments are provided in Appendix Table 3. There are 2 types of follow-up visit: safety follow-up (30 days [± 7 days] after the last dose of study drug) and survival follow-up (every 2 months [± 7 days] after safety follow-up). Patients who discontinue study treatment are to return for an EOT visit for evaluation of safety within 7 days of their last dose or the decision to end study treatment. In addition, patients are to have a safety follow-up telephone call 30 days (± 7 days) after their last dose of study treatment. When an SAE or treatment-related AE is reported during the telephone call, the patient should come to the clinic for physical examination and blood tests, if clinically needed. Follow-up for ongoing SAEs or treatment-related AEs after the safety follow-up visit/call will stop if a patient begins another anticancer therapy. Pregnancy testing will continue monthly up to 6 months after the EOT per the duration of required contraception as discussed in Appendix 5. Testing during survival follow-up may be done at home and the result self-reported by the patient. Survival follow-up will be conducted via a phone call every 2 months until death or end of study. Duration of survival follow-up will be limited to 3 years.

6.11. Assessments for Early Discontinuation From Study

If a patient discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the patient in the study and continue to perform the required study-related follow-up and procedures (Section 6.11.1, Criteria for Discontinuation of Study Treatment*). I*n the absence of disease progression, scans should continue to be collected per Section 6.6 Efficacy Assessment, until disease progression or initiation of systemic antitumor therapy other than the study treatment, whichever is earlier. If this is not possible or acceptable to the patient or investigator, the patient may be withdrawn from the study. For patients who discontinue from the study prior to completion of all protocol-required visits for study assessments or survival -follow-up- as described in the schedule of assessments (Appendix Table 3), the investigator may search publicly available records (where permitted by local laws and regulations) to ascertain survival status unless the patient withdraws consent for such follow-up. This ensures reduced risk of missing critical efficacy data.

6.11.1. Criteria for Discontinuation of Study Treatment

Criteria for discontinuation of study treatment is provided in Section 3.4.

6.12. Criteria for Discontinuation From Study/End of Study

Criteria for discontinuation from study is provided in Section 3.5.

6.13. Poststudy Care

Upon withdrawal from study treatment, patients will receive the care upon which they and their physicians agree. Patients will be followed for disease progression if applicable, survival, and AEs as specified in Appendix Table 1 and Appendix Table 2. Poststudy treatment assessments are described in Appendix Table 3.

6.14. Sample Storage

CCI [redacted]

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 patient administered a study drug that 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.

Preexisting events that increase in severity or change in nature after study drug initiation or as a consequence of participation in the clinical study will also 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 patient 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 patient 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 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 Adverse Event/Serious Adverse Event Clarifications

Given progression of disease is one of the endpoints of the study, in order to maintain study integrity, the following events that are assessed as unrelated to study drug will not be considered AEs/SAEs:

- Progression of disease
- Deaths related to progression of disease

Events that are considered to represent progression of disease should not be recorded as AEs/SAEs unless it is assessed that study drugs contributed to disease progression. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE/SAE.

Death that is attributed by the investigator as solely due to disease progression and that occurs during the protocol-specified AE reporting period should be recorded only on the death eCRF (ie, not collected as an SAE on the AE eCRF).

7.1.2.1.1. Deaths Not Related to Disease Progression

All other deaths (ie, deaths that are not due to disease progression) occurring during the protocol-specified AE reporting period, regardless of attribution, will be recorded on the AE eCRF and reported within 24 hours of awareness and no later than the next business day.

When recording a death on the eCRF, the event or condition that is considered the primary cause of death should be the AE term, and the outcome should be death. A patient can only have 1 AE (SAE) with outcome of death and severity of CTCAE Grade 5.

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 or 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 health care professional, patient, 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 patient.

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 that is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the patient in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the patient has taken the excess dose(s). Overdose cannot be established when the patient cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the patient 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 is defined as 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, or concomitant medication).
- **Yes**: There is reasonable possibility that the event 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 NCI CTCAE, Version 5.0. For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale (Appendix 4).

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, only SAEs related to protocol-mandated procedures are to be reported, using the applicable eCRFs.

7.3.2. Adverse Events

Following initiation of study medication, all AEs, regardless of cause or relationship, will be collected until 30 days after last administration of study drug and reported on the eCRFs as instructed.

All AEs should be followed up 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 initiation of the first dose of study drug and throughout the duration of the study, including the posttreatment follow-up visit, must be reported on the applicable eCRFs and to Gilead Patient Safety (PS) as instructed below

in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the ICF is signed.

Any SAEs and deaths that occur after the posttreatment follow-up visit but within 30 days of the last dose of study drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; 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 PS.

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 visit, must be reported to Gilead PS (Section 7.4.2). Adverse events and SAEs resulting from SSRs must be reported in accordance to the AE and SAE reporting guidance (Section 7.4).

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situations involving a Gilead concomitant therapy (not considered study drug) that occur after the patient first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead PS utilizing the paper SSR form (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Therapy Report

Special situations involving non-Gilead concomitant medications do 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 patient identification, maintaining the traceability of a document to the patient 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 patient'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 PS 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 PS
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

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 PS.

7.4.2. Special Situations Reporting Process

7.4.2.1. Paper Special Situations Reporting Process for Study Drug

All special situations 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 PS from study drug initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

Gilead PS
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

See Section 7.4.2.2 for instructions on reporting special situations with Gilead concomitant medications.

7.4.2.2. Reporting Process for Gilead Concomitant Medications

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

Gilead PS
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

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 patients who are identified after initiation of study drug and throughout the study, including the protocol-required posttreatment follow-up period or 6 months after the last dose of latest administered study treatment, whichever is longer, to Gilead PS using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

In the sacituzumab govitecan cohort only (Safety Run-in Cohort 2 and Phase 2 Cohort 2), the investigator should report pregnancies in female partners of male patients that are identified after initiation of study drug and throughout the study, including the protocol-required posttreatment follow-up period or 3 months after the last dose of sacituzumab govitecan, whichever is longer, to Gilead PS within 24 hours of becoming aware of the pregnancy using the pregnancy report form.

Contact details for transmitting the pregnancy report form are as follows:

Gilead PS
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

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 poststudy must be reported to the Gilead PS.

The patient should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy should be reported to Gilead PS using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PS. Gilead PS contact information is as follows: email: Safety_FC@gilead.com and fax: +1 (650) 522-5477.

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 that may be in the form of line listings, serious adverse drug reactions, or suspected unexpected serious adverse reactions (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 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 (eg, decreased hemoglobin).

Severity should be recorded and graded according to the NCI CTCAE, 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. Abnormal Liver Function Tests

Liver toxicity will be evaluated for all patients.

In the absence of an explanation for increased liver function tests, such as viral hepatitis, pre-existing or acute liver disease, or exposure to other agents associated with liver injury, the patient may be discontinued from the study treatment if the investigator determines that it is not in the patient's best interest to continue. Discontinuation of treatment should be considered if there is an indication of severe liver injury according to Hy's Law, defined by FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation {U.S. Department of Health and Human Services 2009}, as:

- Treatment-emergent ALT or AST elevation (at least 3 × ULN), AND
- Treatment-emergent total bilirubin elevation (more than 2 × ULN), and absence of cholestasis (defined as alkaline phosphatase less than 2 × ULN), AND
- No other good explanation for the injury (hepatitis A, B, C, or other viral hepatic injury, alcohol ingestion, congestive heart failure, worsening liver metastases).

7.8. Toxicity Management

7.8.1. Magrolimab

7.8.1.1. Type and Screen and Direct Antiglobulin Test

Magrolimab may interfere with RBC phenotyping due to expected coating of the RBC membrane. Due to the risk of developing anemia, and because magrolimab may make

phenotyping difficult, ABO/Rh type, antibody screen, blood phenotyping or genotyping, and DAT need to be performed at screening *before exposure to magrolimab*, as described in Section 6.4.2.

Red blood cell phenotyping/genotyping, ABO type, and DAT need not be repeated if results dated before screening are available. Antibody screen need not be repeated if results dated before screening are available, unless the patient was transfused since that time.

7.8.1.2. Anemia, Blood Cross-matching, and Packed Red Blood Cell Transfusion Procedures

Magrolimab binds to RBCs and leads to erythrophagocytosis. CD47 is a member of the Rh complex in the RBC membrane. Therefore, when magrolimab binds to CD47, it is likely to interfere with routine blood bank tests needed in case of transfusion. Notify blood transfusion centers/blood banks of this interference with blood bank testing and inform them that a patient will receive magrolimab.

In clinical studies, anemia is the most common treatment-related AE and is typically manifested as a decline in Hb of about 0.5 to 1.5 g/dL observed in the first 1 to 2 weeks of treatment. This decrease in Hb level had been acceptable in patients with no other significant diseases or medical conditions. However, for patients with significant diseases or medical conditions, such as unstable angina, ischemic heart disease, or uncontrolled diabetes mellitus, treatment-related anemia could be life-threatening or fatal. Significant drops (up to 2 g/dL or higher) have also been observed in early doses.

Within 24 hours prior to each of the first 2 doses of magrolimab infusion during initial treatment, all patients must have a documented hemoglobin ≥ 9 g/dL. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet ≥ 9 g/dL prior to each of the first 2 doses of magrolimab. Patients in South Korea are not permitted to be transfused to meet eligibility criteria (Inclusion Criterion #5a, Exclusion Criterion #4).

Patients with a low baseline Hb level, especially those with cardiac history or risk factors, must be monitored closely after initial administrations of magrolimab as preexisting anemia could be exacerbated. Red blood cell transfusions are permitted prior to study treatment to ensure adequate hemoglobin level as per investigator clinical judgment. This, coupled with anemia from other causes in patients with cancers, means that care must be taken with RBC cross-matching and packed RBC transfusions.

Prior to initiation of magrolimab, ABO/Rh type and screen, DAT, and extended RBC phenotyping (including minor antigens Rh, CcDEe, Cw, MNSs, Kk, Fya, Fyb, Jka, and Jkb) will be performed for each patient. Extended RBC genotyping instead of extended RBC phenotyping is acceptable for any patient. An extended genotype (instead of an RBC phenotype) must be performed if a patient received any RBC or whole blood transfusion within the previous 3 months (unless laboratory has availability for special techniques for performing phenotyping for patients with recent transfusion). Results must be available before the first dose of magrolimab.

For Patients After Exposure to Magrolimab:

An additional hemoglobin must be checked 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment. The patient should be transfused as clinically appropriate. Investigators should consider additional hemoglobin monitoring during the first week of treatment in patients with symptoms of anemia or at increased risk for complications of anemia.

Blood Components for Transfusion:

For all elective RBC and platelet transfusions, use leukocyte-reduced and gamma-irradiated units per institutional guidelines. For RBC transfusions, phenotype/genotype-matched units are preferred. Cytomegalovirus (CMV)-seronegative units for CMV-seronegative patients will not be required for this study.

For instances where the ABO/Rh type cannot be resolved, use pretreatment (historical) phenotype/genotype-matched units for minor RBC antigens (CcDEe and Kk, to the extent feasible). Regarding the ABO type, the institution may use the historical blood group or O type, as per the institutional guidelines.

For emergency transfusions, the transfusion centers may consider using emergency Group O red cells if phenotype/genotype-matched units are not available.

Whenever possible, blood plasma therapy should be blood type specific. Platelets should be blood type compatible whenever possible and, if not, should have been tested and found not to have high titer anti-A or anti-B. Otherwise, plasma and platelet products can be provided as per the institutional policy.

A recent report has suggested that cross-match interference by RBCs due to treatment with magrolimab may be resolved by use of gamma-clone anti-IgG and multiple alloadsorption with papain-treated RBC samples cells, or pooled single donor apheresis platelets, or commercial human platelet concentrate product if required {Troughton 2018, Velliquette 2019}.

7.8.1.3. Management of Infusion-Related Reactions

Infusion-related reactions are defined by the NCI CTCAE, Version 5.0 as “a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances” (Appendix 4). For the purposes of this study, the time frame for IRR assessment is the 24-hour period beginning from the start of the infusion. Premedication use described in Section 5.8 will be used to manage IRRs preemptively.

Recommendations for the management of IRRs are provided below:

- For Grade 1 IRRs, described as mild transient reaction, infusion interruption is not indicated and intervention not indicated:
  - Remain at bedside and monitor patient until recovery from symptoms.

- Patients who experience IRRs with the first 2 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion.

- For Grade 2 IRR, described as requiring symptomatic treatment and prophylactic medications (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, IV fluids) for ≤ 24 hours, infusion interruption is indicated:
  - Stop the magrolimab infusion, begin an IV infusion of normal saline, and consider treating the patient with diphenhydramine 50 mg IV (or equivalent) and/or 500 to 750 mg of oral acetaminophen.
  - Remain at bedside and monitor patient until resolution of symptoms.
  - Corticosteroid therapy may also be given at the discretion of the investigator.
  - If the infusion is interrupted, wait until symptoms resolve, then restart the infusion at 50% of the original infusion rate.
  - If no further complications occur after 1 hour (± 10 minutes), the rate may be increased to 100% of the original infusion rate. Monitor the patient closely.
  - If symptoms recur, stop infusion and disconnect patient from the infusion apparatus. No further magrolimab will be administered at that visit.
  - Patients who experience IRR with the first 2 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion.
  - The amount of magrolimab infused must be recorded on the eCRF.
  - Patients who experience a Grade 2 IRR during the postinfusion observation period that does not resolve to Grade 1 or lower during that time should be observed until the AE resolves or stabilizes, with vital sign measurements as medically indicated for the management of the AE.

- For Grade 3 IRR, described as prolonged reactions or recurrence of symptoms following initial improvement, or where hospitalization is indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates), or Grade 4 IRR, described as having life-threatening consequences, where urgent intervention is indicated:
  - Immediately discontinue infusion of magrolimab.
  - Begin an IV infusion of normal saline and consider treating the patient as follows: Administer bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.

- The patient should be monitored until the investigator is comfortable that the symptoms will not recur.

- Patients who experience Grade 3 IRRs must be given premedication prior to subsequent doses. In this setting, premedication with oral acetaminophen (650 to 1000 mg), oral or IV diphenhydramine (25 to 50 mg), and IV dexamethasone (4 to 20 mg), or a comparable regimen, is recommended for the subsequent 2 doses. Continued premedication with corticosteroids beyond these 2 doses may be administered at the discretion of the treating physician.

- Patients who receive premedication and still experience a recurrent Grade 3 IRR or patients who experience a Grade 4 IRR at any time should be permanently discontinued from the study treatment.

- For anaphylaxis, investigators should follow their institutional guidelines for treatment.

- All patients with Grade 3 or greater IRRs will be observed until the AE resolves or stabilizes, with vital sign measurements and additional evaluations as medically indicated for the management of the AEs.

7.8.1.4. Management of Pneumonitis

Pneumonitis has been infrequently observed in patients receiving magrolimab. Generally, immune-related AEs have not been observed in clinical use with magrolimab. In contrast to T-cell checkpoint inhibitors, magrolimab primarily exerts its antitumor efficacy through macrophage-mediated phagocytosis of tumor cells. Nonspecific T-cell or other host immune responses that are seen with T-cell checkpoint inhibitors have not been observed with magrolimab in nonclinical studies. Additionally, no events of macrophage activation syndrome or hemophagocytic lymphohistiocytosis have been reported in clinical studies.

In instances of suspected pneumonitis, first rule out noninflammatory causes (eg, infections). If a noninflammatory cause is identified, treat accordingly and continue therapy per protocol. Evaluate with imaging, eg chest x-ray or CT, and pulmonary consultation.

Management of potential pneumonitis is detailed in Table 19 and follows ASCO guidelines for immune-related AEs {Brahmer 2018}. Patients who experience Grade 3 to 4 pneumonitis will be permanently discontinued from study treatment.

Table 19. Management of Pneumonitis

Pneumonitis Management Algorithm		
CTCAE Grade of Pneumonitis	**Management**	**Follow-up**
Grade 1 Radiographic changes (CXR or CT) only.	Monitor for signs and symptoms weekly and consider monitoring with CXR. Consider pulmonary and infectious disease consults.	Consider reimaging with CT in 3-4 weeks as clinically indicated. May resume magrolimab with radiographic evidence of improvement or resolution. If no clinical improvement or worsening, treat as Grade 2.
Grade 2 Mild to moderate new symptoms.	Interrupt magrolimab therapy per protocol. Pulmonary and infectious disease consults. Consider empirical antibiotics. Monitor signs and symptoms every 2-3 days; consider hospitalization. 1 mg/kg/day oral prednisone or IV equivalent. Consider bronchoscopy, lung biopsy.	Re-image every 1-3 days. If improving to baseline, taper corticosteroids over 4-6 weeks and resume magrolimab therapy per protocol. If no clinical improvement after 48-72 hours or worsening, treat as Grade 3-4.
Grade 3-4 Severe new symptoms; new/worsening hypoxia; life-threatening.	Discontinue magrolimab therapy. Hospitalize. Pulmonary and infectious disease consults. 1-2 mg/kg/day methylprednisolone IV or IV equivalent. Add empirical antibiotics and consider prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy.	If improving to baseline, taper corticosteroids over 4-6 weeks. If no clinical improvement after 48 hours or worsening, consider additional immunosuppression (eg, infliximab, cyclophosphamide, IV immunoglobulin, mycophenolate mofetil).

CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; CXR = chest x-ray; IV = intravenous

7.8.1.5. Thromboembolic Events

Thromboembolic events, including deep vein thromboses and pulmonary embolisms, have been reported in some patients receiving magrolimab, sometimes early in therapy. Available data for magrolimab do not support a clear or consistent relationship between clinical thromboembolic events and magrolimab use. Patients should be closely monitored for the symptoms of thromboembolic events and treated accordingly.

7.8.1.6. Severe Neutropenia

Prophylaxis

Severe neutropenia and febrile neutropenia were reported in patients treated with magrolimab in combination with chemotherapy. Close monitoring of hematologic parameters (Appendix Table 1 and Appendix Table 2) including neutrophils is required for all patients treated with magrolimab. For patients with high risk of developing Grade 4 neutropenia and febrile neutropenia, primary and secondary prophylaxis with G-CSF is highly recommended. Prophylactic use of antimicrobials may be considered at the discretion of the treating physician.

Management of Neutropenia

- For Grade 3 neutropenia (ANC 500 - 1000/μL) without fever or infection, delay of magrolimab dosing is not recommended.
- For Grade 4 neutropenia (ANC < 500/μL) without fever or infection, or ≥ Grade 3 neutropenia with fever or infection, magrolimab dose delay should be considered. Upon resolution to ≤ Grade 2, resuming magrolimab at the same dose should be considered.
- For persistent severe Grade 4 neutropenia (≥ 7 days) or febrile neutropenia (> 2 occurrences) not attributed to other causes, discontinuation of magrolimab may be considered.
- Treatment with G-CSF should be initiated as soon as clinically indicated.

7.8.1.7. Management of Serious Infections

Patients (with or without neutropenia) should be regularly monitored for signs and symptoms of infection. For patients with prolonged neutropenia or patients at risk, consider infection prophylaxis including antibiotics (eg, fluoroquinolone) or antifungal agents (eg, oral triazoles or parenteral echinocandin) in accordance with current guidelines.

- For patients being treated for serious infections, hold the next dose of magrolimab until the infection has resolved clinically.
- For serious infections that remain active for ≥ 14 days, consider discontinuation of magrolimab.

7.8.2. Nab-paclitaxel and Paclitaxel

Refer to nab-paclitaxel and paclitaxel local prescribing information and local guidelines for safety management. Additional considerations for safety management for nab-paclitaxel and paclitaxel are described in Section 5.3.3.

7.8.3. Sacituzumab Govitecan

For dose reductions and discontinuations for other treatment-related toxicities, please refer to Section 5.15.2. Refer to sacituzumab govitecan local prescribing information and local guidelines for safety management. Additional considerations for safety management are provided below.

7.8.3.1. Gastrointestinal Toxicities

Nausea, vomiting, and diarrhea are frequent sacituzumab govitecan-associated toxicities. Appropriate treatment, including, as needed, fluid and electrolyte replacement, is required to minimize the risk of serious consequences such as dehydration. Instructions for sacituzumab govitecan dose reduction for treatment-related gastrointestinal toxicities are provided in Table 16.

Nausea and Vomiting

Instructions for the use of premedications for prophylactic treatment of nausea and vomiting and anticipatory nausea are provided in Table 15. Do not hold the dose of sacituzumab govitecan for Grade 3 nausea unless Grade 3 nausea persists despite maximal optimal medical management. Patients should be treated for delayed nausea and vomiting on Days 2 and 3 with 5-HT3 receptor antagonist (ondansetron or palonosetron) monotherapy and other agents if needed. Steroids may be added if symptoms do not resolve with these agents. Consider olanzapine for persistent or anticipatory nausea; an olanzapine dose of 2.5 mg or 5 mg at bedtime is recommended. NK1 receptor antagonists (fosaprepitant and aprepitant) may be administered.

Diarrhea

Loperamide should be administered at the onset of treatment-related diarrhea at an initial dose of 4 mg, followed by 2 mg with every episode of diarrhea to a maximum dose of 16 mg/day. If diarrhea is not resolved after 24 hours, add diphenoxylate/atropine or opium tincture as clinically indicated. Add octreotide 100 to 150 µg subcutaneously 3 times per day if diarrhea persists. For Grade 4 diarrhea, consider patient hospitalization and treatment with IV fluids and octreotide.

Antibiotics can be administered as clinically indicated.

Dietary modification should be recommended for the management of diarrhea, including a bland diet, small frequent meals, adequate fluid intake of clear liquids to maintain hydration, and discontinuation of lactose-containing foods and drinks containing alcohol.

Patients who exhibit an excessive cholinergic response to treatment with sacituzumab govitecan (eg, abdominal cramping, diarrhea, salivation) can receive appropriate premedication (eg, atropine) for subsequent treatments.

7.8.3.2. Neutropenia

Sacituzumab govitecan can cause severe or life-threatening neutropenia. Fatal infections in the setting of neutropenia have been observed in clinical trials. Grade 3 or higher neutropenia has been reported in 49% of patients and the median time to first onset of neutropenia (including febrile neutropenia) was 16 days.

- Sacituzumab govitecan should be withheld for ANC < 1500/mm^3 on Day 1 of any cycle or neutrophil count < 1000/mm^3 on Day 8 of any cycle and neutropenic fever.
- Dose modifications of Sacituzumab govitecan may be required due to neutropenia (see Section 5.15 and Table 16). Administer G-CSF as clinically indicated.
- Prophylactic use (primary and secondary) of G-CSF is not mandated but is highly recommended for patients at risk for high grade neutropenia and febrile neutropenia.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

The objectives and endpoints are provided in Section 2.

8.2. Planned Analyses

8.2.1. Dose-Determination Analysis

For the purposes of making the dose de-escalation decisions for the Safety Run-in Cohorts, dose-determination analyses of relevant safety data focusing on DLTs and overall safety profile will be conducted by the sponsor after all patients have completed the required DLT assessment period as specified in Section 3.1.1. Safety assessments (eg, AEs, electrocardiogram, laboratory results) will be displayed by cohort to facilitate the dose de-escalation decisions.

8.2.2. Primary Analysis

For the primary analysis, outstanding data queries will have been resolved or adjudicated as unresolvable, and the data will have been cleaned and finalized for the analysis.

For Phase 2 Cohort 1, the primary analysis of PFS will be conducted after every enrolled patient has a minimum of 6 months follow-up. For Cohort 2 (Safety Run-in Cohort 2 and Phase 2 Cohort 2), the primary analysis of ORR will be conducted when all enrolled patients have approximately a minimum of 6 months follow-up.

8.2.3. Final Analysis

The final analysis may be performed after all patients have completed the study or discontinued early, 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. Efficacy

8.3.1.1.1. Safety Run-in Cohorts

For Safety Run-in Cohorts, the primary analysis set for efficacy analysis is the modified Intent-to-Treat (ITT) Analysis Set, defined as all patients who received at least 1 dose of any study drug.

8.3.1.1.2. Phase 2 Cohort 1

For Phase 2 Cohort 1, the primary analysis set for efficacy analysis is the ITT Analysis Set, defined as all randomized patients according to the treatment arm to which the patients are randomized, unless otherwise specified.

8.3.1.1.3. Cohort 2 (Safety Run-in Cohort 2 and Phase 2 Cohort 2)

For Cohort 2 (Safety Run-in Cohort 2 and Phase 2 Cohort 2), the primary analysis set for efficacy analysis is the modified ITT Analysis Set, defined as all patients who received at least 1 dose of study drug at the selected Phase 2 Cohort 2 dose level. Safety Run-in Cohort 2 and Phase 2 Cohort 2 will be pooled for the endpoint of confirmed ORR in Cohort 2.

8.3.1.2. Safety

8.3.1.2.1. DLT-Evaluable Analysis Set

For Safety Run-in Cohort 1, the primary analysis set for the DLT analysis is the DLT-Evaluable Analysis Set, defined as all patients who meet 1 of the following criteria in the DLT assessment period (defined as 28 days of the first dosing cycle for nab-paclitaxel or paclitaxel):

- The patient experienced a DLT at any time after initiation of the first infusion of magrolimab.
- The patient did not experience a DLT and completed at least 3 infusions of magrolimab (28-day cycle), and at least 2 doses of nab-paclitaxel or paclitaxel in Safety Run-in Cohort 1.

For Safety Run-in Cohort 2, the primary analysis set for the DLT analysis is the DLT-Evaluable Analysis Set, defined as all patients who meet 1 of the following criteria in the DLT assessment period (defined as 21 days of the first dosing cycle for sacituzumab govitecan):

- The patient experienced a DLT at any time after initiation of the first infusion of magrolimab.
- The patient did not experience a DLT and completed at least 2 infusions of magrolimab (21-day cycle), and at least 2 infusions of sacituzumab govitecan in Safety Run-in Cohort 2.

8.3.1.2.2. Safety Run-in Cohorts

For the Safety Run-in Cohorts, the primary analysis set for safety analysis, except for DLTs, is the Safety Analysis Set, defined as all patients who received at least 1 dose of any study drug.

8.3.1.2.3. Phase 2 Cohort 1

For Phase 2 Cohort 1, the primary analysis set for safety analyses is the Safety Analysis Set, defined as all randomized patients who received at least 1 dose of study drug, with treatment assignment designated according to the actual treatment received.

8.3.1.2.4. Phase 2 Cohort 2

For Phase 2 Cohort 2, the primary analysis set for safety analyses is the Safety Analysis Set, defined as all patients who received at least 1 dose of any study drug.

8.3.1.3. Pharmacokinetics

The PK analysis will be conducted on the PK Analysis Set, defined as all patients who received any amount of magrolimab and have at least 1 measurable posttreatment serum concentration of magrolimab.

8.3.1.4. Immunogenicity

The immunogenicity analysis will be conducted on the Immunogenicity Analysis Set, defined as all patients who received any amount of magrolimab and have at least 1 evaluable anti-magrolimab antibody test result.

8.3.1.5. Biomarker

The biomarker analysis will be conducted on the Biomarker Analysis Set, defined as all patients who received any study drug and have at least 1 evaluable biomarker measurement available.

8.3.2. Data Handling Conventions

By-patient listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in analysis set), n (number with data), mean, SD, 95% CIs on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 95% CIs on the percentage. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided. Data will be described and summarized by treatment arm and cohort.

The baseline value used in each analysis will be the last (most recent) pretreatment value before or on the first dosing date of study treatment. As appropriate, changes from baseline to each subsequent time point will be described and summarized. Graphical techniques (ie, waterfall plots, Kaplan-Meier [KM] curves, line plots) may be used when such methods are appropriate and informative. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

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, body mass index, selected laboratory data, medical and cancer history, prior treatment and number of prior treatment(s), tumor imaging for baseline response assessment, randomization stratification group (Phase 2 Cohort 1 only), and ECOG performance status.

8.5. Efficacy Analysis

8.5.1. Primary Efficacy Endpoint Analysis

8.5.1.1. Phase 2 Cohort 1

For Phase 2 Cohort 1, PFS by investigator assessment will be analyzed using KM methods. Patients who did not have documented disease progression or death will be censored at the date of their last response assessment during the study with documentation of no disease progression. The KM estimate of the survival function will be computed, and the results will be presented using KM curves. The median will be provided along with the corresponding 95% CI. A log-rank test may be used to compare treatment difference in PFS. A Cox proportional hazard regression model may be used to estimate the HR and its 2-sided 95% CI.

8.5.1.2. Cohort 2 (Safety Run-in Cohort 2 and Phase 2 Cohort 2)

For Cohort 2 (Safety Run-in Cohort 2 and Phase 2 Cohort 2) patients who are dosed at the selected Phase 2 Cohort 2 dose level, confirmed ORR by investigator assessment with 95% CI based on the Clopper-Pearson method will also be estimated. Patients who do not have sufficient baseline or on-study tumor assessment to characterize response will be counted as nonresponders.

8.5.2. Secondary Efficacy Endpoint Analyses

Analysis of OS and DOR by investigator assessment for Phase 2 Cohort 1 and OS, DOR by investigator assessment, and PFS by investigator assessment for Cohort 2 (Safety Run-in Cohort 2 and Phase 2 Cohort 2) will be similar to the primary endpoint analysis of PFS by investigator assessment for Phase 2 Cohort 1.

Confirmed ORR by investigator assessment for Phase 2 Cohort 1 along with the 95% CI will be estimated based on the Clopper-Pearson method for each treatment group. The chi-square test may be used to compare treatment difference in ORR. Odds ratios and corresponding 95% CIs will also be presented.

8.6. Safety Analysis

8.6.1. Primary Safety Endpoint Analysis

For the Safety Run-in Cohorts, the incidence of DLTs, AEs, and laboratory abnormalities during the DLT assessment period by count and percentage will be reported using the DLT-Evaluable Analysis Set. The DLT assessment period for Safety Run-in Cohort 1 is defined as the first dosing cycle of 28 days. The DLT assessment period for Safety Run-in Cohort 2 is defined as the first dosing cycle of 21 days.

8.6.2. Other Safety Analysis

All safety data collected on or after the date that study drug was first dispensed up to the date of last dose of study drug + 30 days or the day before initiation of new anticancer therapy, whichever is earlier, will be summarized by cohort and treatment arm (according to the study drug received). Data for the pretreatment and treatment-free safety follow-up periods will be included in data listings. For categorical safety data, including incidence of AEs and categorizations of laboratory data, counts and percentages of patients will be summarized. For continuous safety data, including laboratory data, number of patients, mean, SD, minimum, quartiles, median, and maximum will be summarized.

8.6.3. Extent of Exposure

Data regarding a patient's extent of exposure to study drugs will be generated from the study drug administration data. Exposure data will be summarized by cohort and treatment group.

8.6.4. 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. Treatment-emergent adverse events will be defined any AEs with an onset date on or after the date of the first dose of study treatment up to 30 days after the date of the last dose of study treatment, or the day before initiation of subsequent anticancer therapy, whichever comes first.

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

8.6.5. Laboratory Evaluations

Selected laboratory data (using conventional units) will be summarized using only observed data.

Graded laboratory abnormalities will be defined using the grading scheme in Appendix 4.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time point after baseline up to and including the date of last dose of any study drug + 30 days or the day before initiation of new anticancer therapy, whichever is earlier, will be summarized by cohort and treatment group. 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 patient has been discontinued from treatment for at least 30 days or after the day before initiation of new anticancer therapy will be included in a data listing.

8.6.6. Other Safety Evaluations

Vital signs and physical examination findings will be summarized by cohort and treatment group. Details will be provided in the statistical analysis plan.

8.7. Pharmacokinetic Analysis

The PK Analysis Set will be used for summaries of PK concentration of magrolimab versus time. Serum concentrations will be listed and summarized for magrolimab using descriptive statistics by sampling time point and treatment. Graphical plots of individual serum concentration versus time and mean concentration versus time by treatment will be generated. All data from this study may be combined with PK data from other company sponsored clinical studies and analyzed using a population PK model. Such an analysis would be reported separately.

8.8. Immunogenicity Analysis

Immunogenicity will be assessed using a 3-tier (screen, confirmatory, and titer) approach on study samples. The rate and magnitude of anti-magrolimab antibody incidence, prevalence, persistence, and transience will be summarized for the Immunogenicity Analysis Set. Titer summaries may also be generated, if relevant. CCI [redacted]

8.9. Biomarker Analysis

The baseline level, absolute level, and change from baseline level over time will be summarized using descriptive statistics for each biomarker at sample collection time point by cohort and treatment arm, as appropriate. CCI [redacted]

8.10. Analysis of Patient-Reported Outcome Data

Summary statistics and the mean change from baseline of linear-transformed scores will be reported for all of the items and subscales of the EORTC-QLQ-C30, EORTC-QLQ-BR23, and EQ-5D-5L questionnaires at each time point for Cohort 1 only. In addition, mean scores for global health status, physical functioning, and selected symptom scales will be presented. The scores will be derived according to the EORTC scoring manual guidelines.

8.11. Sample Size

Based on the original design, for Phase 2 Cohort 1, using an unstratified log-rank test, a total of 63 PFS events provides 82% power at a 1-sided alpha of 0.15 to detect a HR of 0.61 (assuming median PFS of at least 9 months compared to a control arm median PFS of 5.5 months). Assuming an accrual period of 15 months, a minimum follow-up time of 6 months, and a 5% annual drop-out rate, 92 patients (46 patients per arm) would be required to obtain 63 events.

Due to the early closure of Phase 2 Cohort 1, 28 patients have been enrolled and randomized for Arm A and Arm B. The analysis of the PFS given the current sample size is under powered and will be descriptive only.

For Cohort 2 (Safety Run-in Cohort 2 and Phase 2 Cohort 2), patients treated at the selected Phase 2 Cohort 2 dose level, using chi-square test, a total of 46 patients (including 6 patients in Safety Run-in Cohort 2 and 40 patients in Phase 2 Cohort 2) provides 88% power at a 1-sided alpha of 0.15 to detect an ORR of 50% compared with a null ORR of 34%.

Power calculations were performed using EAST 6.5.

8.12. Gilead Data Review Committee

An internal GDRC will be established to assess the safety of patients in Phase 2 Cohort 1 Arm A and Phase 2 Cohort 2. The GDRC will perform interim reviews of safety data and monitor for treatment-related toxicities as per the prespecified stopping rules in Section 3.1.2.1. Further details of the GDRC's specific activities will be defined in the GDRC charter, as well as the GDRC's membership, conduct, and meeting schedule.

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 (ICH) E6(R2) addendum to its guideline for Good Clinical Practice 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 patient 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 patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study patient 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 patient after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study patients.

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 ICF for documenting written informed consent. Each ICF (or assent as applicable) will be appropriately signed and dated by the patient or the patient'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 patients about genomic testing and/or planned sample retention. In addition to the study-specific ICF to be signed by each patient participating in the study, patients will be required to document agreement to allow the use of the remainder of their already collected specimens for CCI future research, in accordance with applicable regulations. The results of the tests performed on the samples will not be given to the patient or the investigator.

9.1.5. Confidentiality

The investigator must ensure that patients' 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, IRB/IEC, or the laboratory. Laboratory specimens must be labeled in such a way as to protect patient identity while allowing the results to be recorded to the proper patient. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log with details for all patients screened and enrolled in the study, in accordance with the site procedures and regulations. Patient 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, case report forms (CRFs)/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) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, CRFs/eCRFs, IRB/IEC and governmental approval with correspondence, the ICF, 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 patient:

- Patient identification
- Documentation that patient 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 patient 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, and including causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medication (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 patient, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

For each patient consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the electronic data capture (EDC) system. The eCRF casebook will only capture the data required per the protocol schedules of assessments. 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 CRF 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 may be made only by the sponsor.

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 (6 months for pediatric studies, in accordance with Regulation [EC] No. 1901/2006) after the global end of study (as defined in Section 3.5).

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 CRF/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 patient records needed to verify the entries in the CRF/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 patients, appropriate regulatory authority, IRBs, and IECs. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the patients' 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 2 Study of Magrolimab Combination Therapy in Patients With Unresectable, Locally Advanced or Metastatic Triple-Negative Breast Cancer

GS-US-586-6144 Amendment 6; 30 January 2024

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

PPD	*[See appended electronic signature]*
Name (Printed) Medical Monitor	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. Schedules of Assessments

Appendix Table 1. Safety Run-in Cohort 1 and Phase 2 Cohort 1: Schedule of Assessments–Screening and Treatment Period

Visit Window (Days)	Cycle (28-day cycles)												
	Screening Day −30 to −1	1[a]					2[a]				3+[a]		
		None		± 3[b, c]			± 3[b]				± 3[b]		
Cycle Day		1	2	8	15	22	1	8	15	22	1	8	15
Informed consent	X												
Demographics	X												
Medical and cancer history	X												
ECOG	X	X					X				X		
Vital signs, height, and weight[d, e]	X	X		X	X	X	X	X	X	X	X	X	X
Physical examination[e, f]	X	X		X	X	X	X		X		X		X
ECG (single)[g]	X												
Pregnancy test[b, h]	X	X					X				X		
PD-L1[i]	X												
Histology[j]	X												
Hematology[b, c, e]	X	X[c]	X	X[c]	X	X	X	X	X	X	X	X	X
Haptoglobin and LDH[b]		X		X			X						
Serum or plasma chemistry[b, e]	X	X		X	X	X	X	X	X	X	X	X	X
Coagulation[b, k]	X												
Extended RBC phenotyping/genotyping, type and screen (ABO/Rh), DAT	X												
Urinalysis[b,l]	X												
Tumor imaging[m]	X										X, Q8W[n]		
Tumor biopsy	Refer to Appendix Table 4												

Visit Window (Days)	Screening Day −30 to −1	Cycle (28-day cycles)											
		1[a]					2[a]				3+[a]		
		None		± 3[b, c]			± 3[b]				± 3[b]		
Cycle Day		1	2	8	15	22	1	8	15	22	1	8	15
Adverse events[o]	X	→											→
Concomitant medications	X	→											→
Randomization[p]		X											
PRO assessment[q]: EORTC-QLQ-C30, EORTC-QLQ-BR23, and EQ-5D-5L[b] (Phase 2 Cohort 1 only)		X					X				X		
Receptor occupancy	Refer to Appendix Table 4												
Circulating tumor DNA													
PBMC													
Serum and plasma biomarkers													
Whole blood RNA													
Immunophenotyping assay													
TCR sequencing													
Stool microbiome													
Genomic blood sample													
Pharmacokinetics													
Antidrug antibodies													
IRT registration[r]		X		X	X	X	X	X	X	X	X	X	X
Premedication for magrolimab[s]		X		X									
Magrolimab[c, t]		X[c]		X[c]	X	X	X	X	X	X	X		X
Nab-paclitaxel or paclitaxel		X[u]		X	X		X	X	X		X	X	X

ABO = any of the 4 blood groups A, B, AB, and O comprising the ABO system; AE = adverse event; aPTT = activated partial thromboplastin time; CT = computed tomography; DAT = direct antiglobulin test; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire; EORTC-QLQ-BR23 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Breast Cancer Module; EQ-5D-5L = 5-level EuroQol 5 dimensions; INR = international normalized ratio; IRT = interactive response technology; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetics;

PRO = patient-reported outcome; PT = prothrombin time; PTT = partial thromboplastin time; QW = once weekly; Q8W = every 8 weeks; RBC = red blood cell; RECIST = response evaluation criteria in solid tumors; Rh = Rhesus factor; RP2D = recommended Phase 2 dose; TCR = T-cell receptor

c In cases of magrolimab repriming following a treatment delay (Section 5.7), efficacy, biomarker, PK, and immunogenicity assessments should follow the schedule of the assigned cycle number. Magrolimab dosing and the safety assessment should follow Cycle 1 (refer to Table 4 or Table 5 as appropriate), and then subsequently switch back to the next assigned cycle schedule. If repriming is required during Cycles 1 or 2, dosing and safety assessments should follow Cycle 1, then Cycle 2, and then begin maintenance from Cycle 3 onwards. If repriming is required during the maintenance phase (Cycle 3 onwards), magrolimab dosing and safety assessments should follow Cycle 1 and subsequent dosing should resume maintenance dosing at the next assigned cycle. Magrolimab should not be given on consecutive days. Refer to footnote (r) for premedication requirement.

d Pretreatment assessments are to be collected within 24 hours (hemoglobin for the first 2 magrolimab doses per Section 7.8.1.2, PRO assessment) and within 3 days (safety labs) prior to any study treatment administration.

e A complete blood count with differential, platelets, and reticulocytes will be conducted. Within 24 hours prior to each of the first 2 doses of magrolimab infusion during initial treatment, all patients must have a documented hemoglobin ≥ 9 g/dL. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet ≥ 9 g/dL prior to each of the first 2 magrolimab doses. An additional hemoglobin measurement should be performed 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment (Section 7.8.1.2).

f Height will be collected at screening only. Vital sign measurements will be collected predose on the same day as infusion of any study treatment. Weight will be collected at screening and Day 1 of each cycle.

g Vital signs, physical examination, weight, hematology, and serum/plasma chemistry on Cycle 1 Day 2, Cycle 1 Day 22, and Cycle 2 Day 22 should only apply to patients receiving magrolimab.

h Complete physical examination is to be performed at screening and symptom-directed physical examination is to be performed from Cycle 1 Day 1.

i Sites in the United Kingdom should perform additional ECGs once per cycle for the first 3 cycles.

j Serum pregnancy test will be conducted at screening. The Cycle 1 Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was performed within the 72 hours before study treatment administration. Urine or serum pregnancy tests will be conducted from Cycle 1 Day 1.

k PD-L1 to be performed during screening, if a prior diagnostic PD-L1 test result is not available. Testing can be performed locally. If testing not available locally, assessment can be performed using central laboratory.

l After the signing of the informed consent form, histological assessment and documentation of the tumor by local assessment may occur outside of the 30-day screening period.

m The analytes to be tested are PT, INR, and aPTT (or PTT).

n Reflex microscopic testing based on other abnormalities.

o CT/MRI will be performed per Section 6.6. Per RECIST criteria, if a patient achieves an initial objective response (complete response or partial response) on imaging, an imaging assessment at least 4 weeks later is required for confirmed response.

p Visit window: ± 7 days.

q During screening, collect all SAEs considered related to protocol-mandated procedures after signing of the informed consent form.

r Randomization must occur within 30 days of signing informed consent. The first dose on Cycle 1 Day 1 must be within 3 days of randomization.

s If the PRO questionnaires are unavailable in a patient's language, completion is not required. Patients with other barriers to questionnaire completion may be exempt from these assessments after discussion with the sponsor.

t IRT registration will be required for screening, enrollment/randomization, and when dispensing any study drug supplied by Gilead.

u Premedication is required prior to the administration of the first 2 doses of magrolimab and in case of reintroduction with repriming. Premedication should include oral acetaminophen, oral or IV diphenhydramine, and IV dexamethasone, or comparable regimen before the initial 2 doses of magrolimab or in the case of repriming.

v Magrolimab will be administered first before nab-paclitaxel or paclitaxel. Patients to be monitored for 1-hour postinfusion during Cycle 1. Postinfusion monitoring should begin after the infusion is complete, but prior to administering nab-paclitaxel or paclitaxel. Postinfusion monitoring is not required for doses after Cycle 1 Day 22. The RP2D will be determined in Safety Run-in Cohort 1. The magrolimab dosing regimen is described in Table 4 for Safety Run-in Cohort 1 and Table 5 for Phase 2 Cohort 1. If repriming occurs prior to or during the first 2 cycles (8 QW), the patient will have a total of 8 repriming visits starting with 1 mg/kg of magrolimab, then follow the assigned

dose level (eg, 30 mg/kg) for 7 QW (which is Day 8 to Day 50 visits). If repriming occurs at Cycle 3 or onwards, the patient will have a total of 4 repriming visits starting with 1 mg/kg of magrolimab, then follow the assigned dose level (eg, 30 mg/kg) for 3 QW (Day 8 to Day 22 visits). Magrolimab repriming should follow Table 8.
Note: In Safety Run-in Cohort 1 and Phase 2 Cohort 1, if the magrolimab dose is 30 mg/kg from Cycle 3+, magrolimab is not administered on Day 8; refer to Table 4 and Table 5, respectively.

w For patients receiving magrolimab in combination with paclitaxel/nab-paclitaxel, Cycle 1 Day 1 treatment can be administered over 2 days such that magrolimab is administered on Cycle 1 Day 1 and paclitaxel/nab-paclitaxel on Cycle 1 Day 2. This also applies to repriming cycles that require Cycle 1 Day 1 dosing of magrolimab. Cycle 1 Day 1 dosing and infusion time requirements for each agent should be followed, as listed in Table 4 and Table 5. Premedication guidelines should be followed prior to magrolimab (see Section 5.8), paclitaxel/nab-paclitaxel (see Section 5.11). Patients should be observed during and following the infusion for signs or symptoms of infusion-related reactions (see Section 5.6 for magrolimab and Section 5.10 for paclitaxel/nab-paclitaxel).
Note: Refer to Section 6.5, Safety Assessments, for complete list of analytes to be tested.

Appendix Table 2. Safety Run-in Cohort 2 and Phase 2 Cohort 2: Schedule of Assessments–Screening and Treatment Period

Visit Window (Days)	Screening Day −30 to −1	Cycle (21-day cycles)								
		1[a]				2[a]			3+[a]	
		None		± 3[b, c]		± 3[b]			± 3[b]	
Cycle Day		1	2	8	15	1	8	15	1	8
Informed consent	X									
Demographics	X[d]									
Medical and cancer history	X[d]									
ECOG[d]	X[d]	X				X			X	
Vital signs, height, and weight[e]	X[d]	X		X	X	X	X	X	X	X
Physical examination[f]	X	X		X	X	X		X	X	
ECG (single)[g]	X									
Pregnancy test[b, h]	X[d]	X				X			X	
PD-L1[i]	X									
Histology[j]	X									
Hematology[b, c]	X[d]	X[c]	X	X[c]	X	X	X	X	X	X
Haptoglobin and LDH[b]		X		X		X				
Serum or plasma chemistry[b]	X[d]	X		X	X	X	X	X	X	X
Coagulation[b, k]	X									
Extended RBC phenotyping/genotyping, type and screen (ABO/Rh), DAT	X[d]									
Urinalysis[b, l]	X									
Tumor imaging[m]	X[d]								X, Q6W[n]	
Tumor biopsy	Refer Appendix Table 4									
Adverse events[o]	X[p]	→								→
Concomitant medications	X[d]	→								→

Visit Window (Days)	Cycle (21-day cycles)									
	Screening Day −30 to −1	1[a]				2[a]			3+[a]	
		None		± 3[b, c]		± 3[b]			± 3[b]	
Cycle Day		1	2	8	15	1	8	15	1	8
Receptor occupancy	Refer to Appendix Table 4									
Circulating tumor DNA										
PBMC										
Serum and plasma biomarkers										
Whole blood RNA										
Immunophenotyping assay										
TCR sequencing										
Stool microbiome										
Genomic blood sample										
Pharmacokinetics										
Antidrug antibodies										
IRT registration[q]		X		X	X	X	X	X	X	X
Premedication for magrolimab[r]		X		X						
Magrolimab[c, s]		X[c]		X[c]	X	X	X	X	X	
Premedication for sacituzumab govitecan		X		X		X	X		X	X
Sacituzumab govitecan		X[t]		X		X	X		X	X

ABO = any of the 4 blood groups A, B, AB, and O comprising the ABO system; AE = adverse event; aPTT = activated partial thromboplastin time; CT = computed tomography; DAT = direct antiglobulin test; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; IRT = interactive response technology; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; QW = once weekly; Q6W = every 6 weeks; RBC = red blood cell; RECIST = response evaluation criteria in solid tumors; Rh = Rhesus factor; RP2D = recommended Phase 2 dose; TCR = T-cell receptor.

a In cases of magrolimab repriming following a treatment delay (Section 5.7), efficacy, biomarker, PK, and immunogenicity assessments should follow the schedule of the assigned cycle number. Magrolimab dosing and the safety assessment should follow Cycle 1 (refer to Table 6 or Table 7 as appropriate), and then subsequently switch back to the next assigned cycle schedule. If repriming is required during Cycles 1 or 2, dosing and safety assessments should follow Cycle 1, then Cycle 2 and begin maintenance from Cycle 3 onwards. If repriming is required during the maintenance phase (Cycle 3 onwards), magrolimab dosing and safety assessments should follow Cycle 1 and subsequent dosing should resume maintenance dosing at the next assigned cycle. Magrolimab should not be given on consecutive days. Refer to footnote (q) for premedication requirement.

b Pretreatment assessments are to be collected within 24 hours (hemoglobin for the first 2 magrolimab doses per Section 7.8.1.2) and within 3 days (safety labs) prior to any study treatment administration.
c A complete blood count with differential, platelets, and reticulocytes will be conducted. Within 24 hours prior to each of the first 2 doses of magrolimab infusion during initial treatment, all patients must have a documented hemoglobin ≥ 9 g/dL. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet ≥ 9 g/dL prior to each of the first 2 magrolimab doses. An additional hemoglobin measurement should be performed 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment (Section 7.8.1.2).
d Assessment results for patients enrolled in Cohort 1 Arm B with documented progressive disease that rescreen to enroll in Cohort 2 can be used for screening, if within the required screening period.
e Height will be collected at screening only. Vital sign measurements will be collected predose on the same day as infusion of any study treatment. Weight will be collected at screening and Day 1 of each cycle.
f Complete physical examination is to be performed at screening and symptom-directed physical examination is to be performed from Cycle 1 Day 1.
g Sites in the United Kingdom should perform additional ECGs once per cycle for the first 3 cycles.
h Serum pregnancy test will be conducted at screening. The Cycle 1 Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was performed within the 72 hours before study treatment administration. Urine or serum pregnancy tests will be conducted from Cycle 1 Day 1.
i PD-L1 to be performed during screening, if a prior diagnostic PD-L1 test result is not available. Testing can be performed locally. If testing not available locally, assessment can be performed using central laboratory.
j After the signing of the informed consent form, histological assessment and documentation of the tumor by local assessment may occur outside of the 30-day screening period.
k The analytes to be tested are PT, INR, and aPTT (or PTT).
l Reflex microscopic testing based on other abnormalities.
m CT/MRI will be performed per Section 6.6. Per RECIST criteria, if a patient achieves an initial objective response (complete response or partial response) on imaging, an imaging assessment at least 4 weeks later is required for confirmed response.
n Every 6 weeks through 36 weeks (Weeks 6, 12, 18, 24, 30, and 36), then every 9 weeks. Visit window: ± 7 days.
o During screening, collect all SAEs considered related to protocol-mandated procedures after signing of the informed consent form.
p For patients enrolled in Cohort 1 Arm B with documented progressive disease that rescreen to enroll in Cohort 2, AEs should be reported under their Cohort 1 patient ID until they receive the first treatment dose in Cohort 2, and ongoing AEs from Cohort 1 should be captured as medical history.
q IRT registration will be required for screening, enrollment/randomization, and when dispensing any study drug supplied by Gilead.
r Premedication is required prior to the administration of the first 2 doses of magrolimab and in case of reintroduction with repriming. Premedication should include oral acetaminophen, oral or IV diphenhydramine, and IV dexamethasone, or comparable regimen before the initial 2 doses of magrolimab or in the case of repriming.
s Magrolimab will be administered first before sacituzumab govitecan. Patients to be monitored for 1-hour postinfusion during Cycle 1. Postinfusion monitoring should begin after the infusion is complete, but prior to administering sacituzumab govitecan. Postinfusion monitoring is not required for doses after Cycle 1 Day 15. The RP2D will be determined in Safety Run-in Cohort 2. The magrolimab dosing regimen is described in Table 6 for Safety Run-in Cohort 2 and Table 7 for Phase 2 Cohort 2. If repriming occurs prior to or during the first 2 cycles (6 QW), the patient will have a total of 6 repriming visits starting with 1 mg/kg of magrolimab, then follow the assigned dose level (eg, 30 mg/kg) for 5 QW (which is Day 7 to Day 36 visits). If repriming occurs at Cycle 3 or onwards, the patient will have a total of 3 repriming visits starting with 1 mg/kg of magrolimab, then follow the assigned dose level (eg, 30 mg/kg) for 2 QW (Day 8 to Day 15 visits). Magrolimab repriming should follow Table 9.
t For patients receiving magrolimab in combination with sacituzumab govitecan, Cycle 1 Day 1 treatment can be administered over 2 days such that magrolimab is administered on Cycle 1 Day 1 and sacituzumab govitecan on Cycle 1 Day 2. This also applies to repriming cycles that require Cycle 1 Day 1 dosing of magrolimab. Cycle 1 Day 1 dosing and infusion time requirements for each agent should be followed, as listed in Table 6 and Table 7. Premedication guidelines should be followed prior to magrolimab (see Section 5.8) and sacituzumab govitecan (see Section 5.14). Patients should be observed during and following the infusion for signs or symptoms of infusion-related reactions (see Section 5.6 for magrolimab and Section 5.13 for sacituzumab govitecan).
Note: Refer to Section 6.5, Safety Assessments, for complete list of analytes to be tested.

Appendix Table 3. Schedule of Assessments–Posttreatment

	EOT Visit	Safety Follow-up Visit/Call (Telephone)[a]	Pre-Progression Visit[b]	Survival Follow-up
	Within 7 Days After Last Dose or EOT Decision	30 Days After Last Dose	After Safety Follow-Up Until Disease Progression	Every 2 Months After Safety Follow-Up
Visit Window	± 7 Days	± 7 Days		± 7 Days
Urine or serum pregnancy test[c]	X	X	X	
Hematology[d]	X			
Serum or plasma chemistry	X			
Pharmacokinetics	Refer to Appendix Table 4			
Antidrug antibodies				
Tumor imaging for response assessment[e]	X		X	
ECOG	X			
Vital signs	X			
Symptom-directed physical examination	X			
ECG (UK sites only)	X			
PRO assessment[f]	X			
Receptor occupancy	Refer to Appendix Table 4			
Circulating tumor DNA				
Serum and plasma biomarkers				
Whole blood RNA				
Adverse events[g]	X	X		
Concomitant medications	X	X		
New anticancer therapy		X	X	X[h]
Survival follow-up				Every 2 months[i]

AE = adverse event; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; MRI = magnetic resonance imaging; PRO = patient-reported outcome; SAE = serious adverse event

a If the patient experiences a treatment-related AE or an SAE (regardless of attribution), the patient must be asked to come to the site.

b This will only apply for patients who stop study treatment in the absence of disease progression per RECIST, Version 1.1 and will continue to have tumor imaging. See footnote (e) for details on tumor imaging schedule. Pre-progression visits will be completed first before proceeding to survival follow-up.

c Pregnancy testing will continue monthly up to 6 months after the EOT per the duration of required contraception as discussed in Appendix 5. Testing during survival follow-up may be done at home and the result self-reported by the patient.

d A complete blood count with differential, platelets, and reticulocytes will be conducted.

e Tumor imaging at EOT visit not required if performed within the last 30 days or progressive disease per RECIST, Version 1.1 has been documented. CT/MRI will be performed per Section 6.6. For patients who stop study treatment in the absence of disease progression per RECIST, Version 1.1 (eg, experienced unexpected toxicity), scans should continue to be collected approximately every 8 weeks (28-day dosing cycle) for Cohort 1 patients and every 9 weeks (21-day dosing cycle) for Cohort 2 patients until disease progression or initiation of systemic antitumor therapy other than the study treatment, whichever is earlier.
f PRO assessments will be conducted for patients in Phase 2 Cohort 1 only. If the PRO questionnaires are unavailable in a patient's language, completion is not required. Patients with other barriers to questionnaire completion may be exempt from these assessments after discussion with the sponsor.
g Report all AEs through the Safety Follow-up Visit/Call, and any treatment-related SAEs thereafter.
h Collect new anticancer therapy data following the last dose of study treatment until the end of survival follow-up.
i Survival follow-up will be conducted via a phone call every 2 months until death or end of study. Duration of survival follow-up will be limited to 3 years.

Appendix Table 4. Cohort 1 and Cohort 2: Schedule of Assessments–Pharmacokinetic, Antidrug Antibodies, and Biomarker

	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 7	Cycle 10	Cycle 13	EOT
Cycle Day	**Day −30 to −1**	**1**	**8**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
PK[a]		X	X		X	X[b]		X	X	X	X	X
Antidrug antibodies[c]		X			X	X		X	X	X	X	X
Receptor occupancy[d]		X	X	X		X	X	X		X		X
Circulating tumor DNA[e]	X[f]	X		X		X	X		X			X
PBMC[g]		X	X		X	X						
TCR sequencing[g]		X	X		X	X						
Immunophenotyping assay[g]		X	X[h]		X	X						
Serum and plasma biomarkers[i]		X	X[h]		X	X	X		X			X
Whole blood RNA[i]		X	X[h]		X	X	X		X			X
Stool microbiome[j]		X										
Genomic blood sample[k]		X										
Tumor biopsy	X[l]					X[m]						

ADA = antidrug antibodies; EOT = end of treatment; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RO = receptor occupancy; TCR = T-cell receptor

a PK samples will be collected from patients who are assigned to receive magrolimab. PK samples are to be collected predose within 12 hours prior to the first administration of magrolimab given in Cycles 1, 2, 3, 5, 7, 10, 13, and on Cycle 1 Day 8, and at the EOT.

b In Cycle 3, PK samples are to be collected predose (within 12 hours) and postdose at 1 hour (± 15 min) after the end of the infusion of the first administration of magrolimab given.

c ADA samples will be collected from patients who are assigned to receive magrolimab. ADA samples are to be collected prior to the administration of magrolimab at the same time as the predose PK samples in Cycles 1, 2, 3, 5, 7, 10, 13, and at the EOT.

d RO samples will be collected from patients who are assigned to receive magrolimab. RO samples are to be collected predose within 12 hours prior to administration of magrolimab on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15, predose within 12 hours prior to the first administration of magrolimab given in Cycles 3, 4, 5, and 10, and at EOT, if occurring before Cycle 10. RO samples will be collected at select sites only.

e Samples will be collected at screening and predose within 12 hours prior to the administration of any study drug on Cycle 1 Day 1 and Cycle 1 Day 15, predose within 12 hours prior to the first administration of any study drug given in Cycles 3, 4, and 7, and at EOT (regardless of time of occurrence).

f Assessment results for patients enrolled in Cohort 1 Arm B with documented progressive disease that rescreen to enroll in Cohort 2 can be used for screening if within the required screening period.

g Samples will be collected predose within 12 hours prior to administration of any study drug on Cycle 1 Day 1 and Cycle 1 Day 8, and predose within 12 hours prior to the first administration of any study drug given in Cycles 2 and 3. PBMC and immunophenotyping will be collected at select sites only.
h For patients receiving magrolimab, an additional sample for serum and plasma biomarkers, whole blood RNA, and immunophenotyping assay will be collected 4 hours after the start of magrolimab administration on Cycle 1 Day 8.
i Samples will be collected predose within 12 hours prior to administration of any study drug on Cycle 1 Day 1 and Cycle 1 Day 8, predose within 12 hours prior to the first administration of any study drug given in Cycles 2, 3, 4, and 7, and at EOT if occurring before Cycle 7.
j Stool microbiome to be collected predose on or before Cycle 1 Day 1.
k The genomic blood sample can be collected at Cycle 1 Day 1 or at any time during the study. Patients enrolled in Cohort 1 Arm B with documented progressive disease that rescreen to enroll in Cohort 2 do not need to submit a new sample under Cohort 2 patient ID.
l For patients enrolled in Cohort 1 Arm B with documented progressive disease that rescreen to enroll in Cohort 2, a new tumor biopsy at the time of rescreening should be obtained fresh whenever possible. Alternatively, tissue from on-treatment biopsy submitted as part of Cohort 1 assessments can be accepted, if available.
m On-treatment tumor biopsy can be collected any time between Cycle 3 Day 1 and Cycle 4 Day 1.

Appendix 3. Pandemic Risk Assessment and Mitigation Plan

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

These potential risks and mitigation plans can be summarized as follows:

1) Schedule of assessments:

   a) Physical examination:

      In order to limit a patient's time in the clinic, a virtual visit may be conducted for the physical examination assessment. Vital signs may be omitted for virtual visits. However, dosing and biological sample collection should occur per protocol in the clinic.

   b) Dosing:

      Patients may be unable to return to the site for a number of visits to receive the study drug, or the site may be unable to accept any patient visits. Without study drugs, the patient would not be able to stay on the study drug as planned per protocol.

      Mitigation plan: If permitted by local ethics committee/institutional review boards noninvestigational product as determined by sponsor (ie, nab-paclitaxel or paclitaxel) can be administered at a clinic closer to the patient, under the supervision of a licensed physician. If necessary, a dosing delay for magrolimab must be discussed with the sponsor in this instance. A virtual study visit, via phone or video conferencing, must be performed prior to remote dosing. At the earliest opportunity, the site will schedule in-person patient visits and return to the protocol's regular schedule of assessments. A qualified courier may be considered to ship the drug from sites to the alternate clinic.

   c) General patient selection guidance:

      To minimize patients receiving red blood cell transfusions, we recommend selecting patients with higher hemoglobin thresholds at baseline and use intravenous iron and/or erythropoietin where clinically indicated.

2) Study drug supplies to patients and sites:

   Shipments of study drug from the sponsor to the investigational site could be delayed because of transportation issues. Without study drug, the patient 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.

3) Patient safety monitoring and follow-up:

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

      Mitigation plan: For patients 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 patient within the target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

      i) Confirm if patient 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

      iii) If applicable, confirm that patient-reported outcomes have been completed and transmitted where possible

   b) Patients may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence, samples may not be analyzed at the site laboratory and/or sent for central laboratory analyses.

      Mitigation plan: Accredited local laboratories that are not affiliated with the site may be utilized as appropriate to monitor patient safety until the patient can return to the site for their regular follow-up per protocol. Any laboratory assessments conducted at a local laboratory due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible. Alternative sample handling and storage may be possible for samples routinely sent to the central laboratory, sites should refer to the Study Laboratory Manual and discuss with the sponsor for further guidance.

   c) Patients may be unable or unwilling to attend the study visit to sign an updated informed consent form version if there is an update.

      Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local EC/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.

   d) The safety of study patients is important and testing of COVID-19 infection will be based on local clinical guidelines for testing based on signs/symptoms and or suspected exposure to COVID-19.

Mitigation plan: If patient has a diagnosis of COVID-19 while on this clinical study, study drugs may be held until clinical improvement or resolution in accordance with the treating physician's judgment and general magrolimab dose delay guidance in the protocol. Additional supportive care and treatment measures for COVID-19 infection on the study will be performed in accordance with local institutional guidelines. Patients with a COVID-19 infection while participating in a clinical study will have this event documented as an adverse event in the clinical database.

4) 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 patient visits or deviation to the protocol due to the pandemic must be reported in the electronic case report form 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, source data verification, or study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in source data verification, 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. 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 patients on site must be tracked centrally and updated on a regular basis.

5) Missing data and data integrity:

   a) There may be an increased amount of missing data due to patients 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.

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 alternative methods that will ensure the evaluation and assessment of the safety of patients 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 magrolimab in study patients remains unchanged. In case of an increase in these potential risks which cannot be mitigated due to the escalation of a pandemic, enrollment/randomization of new patients will be placed on hold until the pandemic outbreak is under control by following local regulatory guidelines.

Appendix 4. Toxicity 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 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 patient is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal, unless the patient is permanently sterile or has medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are at least 54 years of age with cessation of previously occurring menses for at least 12 months without an alternative cause. In addition, women of less than 54 years of age with amenorrhea of at least 12 months may also be considered postmenopausal if their follicle-stimulating hormone 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 patient of any age.

b. Definition of Male Fertility

For the purposes of this study, a male-born patient is considered fertile after the initiation of puberty unless the patient is permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Patients

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Magrolimab is contraindicated in pregnancy as a higher incidence of total pregnancy loss has been observed in an embryo-fetal development toxicity study in cynomolgus monkeys and there is a strong suspicion of human fetotoxicity in early pregnancy based on nonclinical data. For magrolimab, there is no anticipated pharmacokinetic interaction with progestin or other steroids based on the distinct clearance pathways.

Based on the MOA and findings in animals, nab-paclitaxel or paclitaxel can cause fetal harm when administered to a pregnant woman. There is no contraindication to hormonal contraception according to the nab-paclitaxel or paclitaxel prescribing information.

Sacituzumab govitecan is contraindicated in pregnancy because a malformative effect has been demonstrated/suspected or is unknown, taking into consideration class effects, and genotoxic potential. Based on the assessment of published data related to cytochrome P450 enzyme inhibition and induction experiments for SN-38, efficacy of hormonal contraception is not expected to be impacted due to sacituzumab govitecan administration. A dedicated oral contraceptive drug-drug interaction clinical study has not been conducted. Refer to the latest version of the investigator's brochure for additional information.

b. Contraception Requirements for Female Patients of Childbearing Potential

The inclusion of female patients of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of less than 1% per year. They must have a negative serum pregnancy test at screening and a negative pregnancy test is required prior to study treatment administration on Cycle 1 Day 1. The Cycle 1 Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was performed within the 72 hours before study treatment administration. Pregnancy tests will be performed at the beginning of each cycle thereafter (described in the protocol) and continue monthly up to 6 months after the end of treatment per the duration of required contraception.

Duration of required contraception for female patients in this clinical study should start from screening visit until 6 months after last dose of the latest administered study drug.

Female patients 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 patient's preferred and usual lifestyle.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below:
  - Nonhormonal intrauterine device (IUD)
  - Hormonal IUD (must be used in conjunction with a barrier method)
  - Bilateral tubal occlusion (upon medical assessment of surgical success)
  - Vasectomy in the male partner (upon medical assessment of surgical success)

Or

Female patients 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

- 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 patients must also refrain from egg donation, cryopreservation of cells, and in vitro fertilization during treatment and until the end of contraception requirement. If needed, female patients should be advised to seek advice about egg donation and cryopreservation prior to treatment.

3) Contraception Requirements for Male Patients

It is theoretically possible that a relevant systemic concentration of study drug may be achieved in a female partner from exposure to the patient's seminal fluid and pose a potential risk to an embryo/fetus. Male patients with female partners of childbearing potential must use condoms during treatment and until 6 months after last dose of the latest administered study drug. If the female partner of childbearing potential is not pregnant, use of any locally approved contraceptive measure should also be considered.

Male patients must also refrain from sperm donation and cryopreservation of cells during treatment and until the end of contraception requirement. If needed, male patients should be advised to seek advice about sperm donation and cryopreservation prior to 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 patients 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 patients whose partner has become pregnant or suspects she is pregnant from start of study to 6 months after last study drug dose must also report the information to the investigator. Partner pregnancy information will only be collected for the sacituzumab govitecan cohort (Cohort 2) in this study (throughout the study or for 3 months after the last dose of sacituzumab govitecan, whichever is longer); however, the investigator should reinforce proper contraception use with the study patient if a partner pregnancy is reported in any cohort.

Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.4.2.3.

Appendix 6. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire (EORTC-QLQ-C30) and Breast Cancer Module (EORTC-QLQ-BR23)

https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-QLQ-C30-English.pdf

https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-BR23-English-1.1.pdf

Appendix 7. 5-Level EuroQol 5 Dimensions Questionnaire (EQ-5D-5L)

Health Questionnaire

English version for the UK

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

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

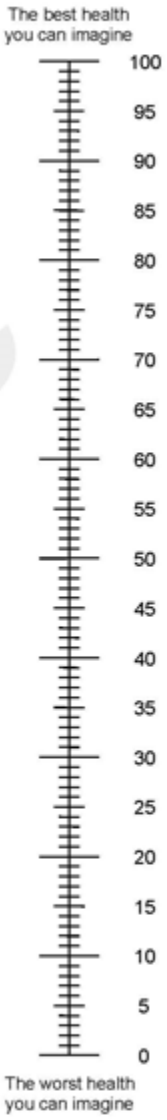
ANXIETY / DEPRESSION

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

2

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

YOUR HEALTH TODAY = ☐



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Appendix 8. Eastern Cooperative Oncology Group (ECOG) Performance Status

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

{Oken 1982}

Appendix 9. American Society of Clinical Oncology/College of American Pathologists Guidelines

Appendix 10. Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.1)

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (Version 1.1). *Eur J Cancer*. 2009;45:228-247 for full RECIST guidelines.

Appendix 11. UGT1A1 Inducers and Inhibitors

Inducers of UGT1A1	Inhibitors of UGT1A1
Carbamazepine	Amitriptyline
Efavirenz	Atazanavir
Ethinylestradiol	Dacomitinib
Lamotrigine	Dasabuvir
Phenobarbital	Deferasirox
Phenytoin	Eltrombopag
Primidone	Enasidenib
Rifampicin	Erlotinib
Ritonavir	Flunitrazepam
Tipranavir	Flurbiprofen
	Fostamatinib
	Gemfibrozil
	Glecaprevir
	Indinavir
	Indomethacin
	Ketoconazole
	Nilotinib
	Ombitasvir
	Paritaprevir
	Pazopanib
	Pexidartinib
	Pibrentasvir
	Probenecid
	Propofol
	Regorafenib
	Rucaparib
	Silibinin
	Sorafenib
	Valproic acid

UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1

Appendix 12. Country-Specific Requirements

Additional Country-Specific Requirements for United Kingdom (UK)

Country-specific Requirements	Protocol Section
Patients with a history of noninfectious pneumonitis or patients with current pneumonitis are excluded. Patients who must continue therapies that are prohibited while receiving paclitaxel or nab-paclitaxel are excluded.	Synopsis, Section 4.3
To increase cardiac monitoring for paclitaxel-related events or the possibility of exacerbation of cardiac events due to magrolimab-related anemia, additional electrocardiogram assessments should be performed once per cycle for the first 3 cycles and at the end of treatment.	Section 6.4.6

Additional Country-Specific Requirements for South Korea

Country-specific Requirements	Protocol Section
Patients in South Korea are not permitted to be transfused to meet eligibility criteria for hemoglobin.	Synopsis, Sections 4.2, 4.3, and 7.8.1.2.

Appendix 13. Amendment History

High-level summaries of the history of this study's amendments are provided in tabular form in the subsections below (from most recent amendment to oldest). Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

Separate summary of change documents for earlier amendments are available upon request.

A separate tracked change (red-lined) document comparing the Amendment 5 to this amendment will be made available upon the publication of this protocol.

Amendment 6 (30 January 2024)

Rationale for Key Changes Included in Amendment 6	Affected Sections
Clarified that due to early closure of Phase 2 Cohort 1, the primary analysis of Phase 2 Cohort 1 is no longer event driven but will occur once every enrolled patient has a minimum of 6 months follow-up.	Synopsis, Sections 3.1.2 and 8.2.2
Updated the efficacy analysis in Phase 2 Cohort 1 due to underpowered sample size.	Synopsis, Section 8.5.1.1, Section 8.5.2
Updated the sample size justification in Phase 2 Cohort 1 to describe the current design on account of early closure of Phase 2 Cohort 1.	Synopsis, Study schema, and Section 8.11
Updated the methodology to allow the evaluation of probability of early stop of the study treatment at any given true toxicity rate. Threshold values have also been updated based on maximum acceptable toxicity rate of combination therapies. These changes have been made considering the trade-off between the early stoppage chance for the unacceptable rates of potential synergistic toxicities and the likelihood for early stoppage while true toxicity rate is acceptable.	Section 3.1.2.1
Removed the second Gilead Data Review Committee (GDRC) given the early closure of Phase 2 Cohort 1.	Section 3.1.2.1
Updated the sacituzumab govitecan (SG) administration window for Cycle 1 Day 1 per SG content library and SG Pharmacy Manual update.	Table 7
Updated the number of patients enrolled in the study and Phase 2 Cohort 1	Synopsis, Section 4.1
Clarified that the final analysis may be performed but not required.	Section 8.2.3
Minor changes to correct typographic errors.	Throughout, as needed

Amendment 5 (30 October 2023)

Rationale for Key Changes Included in Amendment 5	Affected Sections
Clarification of timing of treatment-related toxicity monitoring.	Section 3.1.2.1
Clarification for continuation of study drug treatment in the event of disease progression.	Sections 3.3 and 3.4
Clarification of TNBC disease status and prior lines of therapy in Inclusion Criteria 12 and 15 and Exclusion criterion 20.	Synopsis, Sections 4.2 and 4.3

Rationale for Key Changes Included in Amendment 5	Affected Sections
Clarification of Exclusion Criterion 3 related to active CNS disease.	Synopsis, Section 4.3
Country-specific requirements and cross-references added to provide to specific guidance and requirements for sites in the United Kingdom and South Korea.	Synopsis, Section 4.3, Section 6.4.6, Appendix Tables 1, 2, and 3, Appendix 12
Clarification of Exclusion Criterion 16 related to active uncontrolled infection.	Synopsis, Section 4.3
Clarification of exception to exclusion criteria related to patients with controlled hypo- or hyperthyroidism, or other endocrinopathies.	Synopsis, Section 4.3
Storage requirements for sacituzumab govitecan updated.	Section 5.5.3
Removed requirement for sponsor approval to withhold magrolimab for treatment-emergent and/or -related AEs.	Section 5.7
Guidance for the use of corticosteroids as premedication for the first 2 doses of magrolimab or in the case of repriming provided.	Section 5.8, Appendix Tables 1, and 2
Guidance provided for use of granulocyte-colony stimulating factor as prophylaxis for neutropenia associated with sacituzumab govitecan.	Section 5.14, Table 15, and Section 5.15
Clarification of dose modification for sacituzumab govitecan and action to be taken in the case of severe neutropenia.	Table 16
Clarification of specific SAE collection between obtaining informed consent and first dose of study drug.	Section 6.2.2, Section 7.3.3, Appendix Tables 1 and 2
Clarification of criteria for pregnancy testing requirements.	Section 6.10, Appendix Table 3
Clarification of the timing of PRO instrument administration.	Section 6.4.7
Requirement of a brain MRI with contrast for all patients at screening added.	Section 6.6
Clarification of disease progression criteria added.	Section 6.6, Appendix Table 3
Updated guidance provided for management of infusion-related reactions.	Section 7.8.1.3
Sections added for guidance on management of severe neutropenia and serious infections.	Sections 7.8.1.6 and 7.8.1.7
Section added for guidance on management of neutropenia.	Section 7.8.3.2
Findings from nonclinical study incorporated into pregnancy precaution guidance.	Appendix 5
Minor changes to correct typographic errors.	Throughout, as needed

Amendment 4 (07 March 2023)

Rationale for Key Changes Included in Amendment 4	Affected Sections
Secondary objectives and endpoints were updated to remove independent central review for objective response rate, progression-free survival, and duration of response assessments.	Synopsis and Sections 2 and 6.6
Requirement for prior lines of treatment updated to be more inclusive of patient population.	Synopsis, Study Schema, Section 3.1
Clarified assessments that can be utilized for screening.	Section 3.1
Optional prescreening collection added for sample collection.	Section 6.2.1
Clarification added for timing of drug administration for patients receiving combination therapy.	Sections 3.2.2, 5.6, 5.10, and 5.13.1, Appendix Tables 1 and 2
Clarification added that patient-reported outcome assessments can be waived if there is a barrier to completion.	Section 6.4.7, Appendix Tables 1 and 3
Circulating tumor cell sample collection was removed from biomarker assessment.	Section 3.8, Appendix Tables 1 and 2
Eligibility updated to allow patients enrolled in another trial who are not receiving a therapeutic intervention.	Synopsis, Sections 4.1, 4.3, and 6.2.2, and Appendix Tables 2 and 4
Eligibility criteria updated for change in number of prior treatments allowed.	Synopsis, Section 4.2
Packaging and handling of sacituzumab govitecan updated to align with current practice.	Sections 3.2.2 and 5.5.3
Clarification added that patients do not need to come to clinic for certain assessments if not receiving magrolimab.	Appendix Table 1
Clarification added regarding sourcing and labeling of non-Gilead study medications.	Sections 5.3.2 and 5.4.2
Clarification added regarding repriming sequence of dosing and safety assessments.	Section 5.7 (Tables 8 and 9) and Appendix Tables 1 and 2
Footnotes were removed from Tables 11, 12, 13 and 14 because there is no dose de-escalation of nab-paclitaxel and paclitaxel in the Safety Run-in Cohorts.	Sections 5.12.1, 5.12.2, 5.12.3, and 5.12.5
Stool microbiome assessment removed for Cycle 3 Day 1.	Appendix Table 4
Window for collection of safety data following study drug administration updated for initiation of new anticancer therapy.	Section 8.6.2
Timing of the primary analysis updated for clarity.	Section 8.2.2
Pregnancy test removed from survival follow-up to align with guidance from last treatment.	Section 6.10, Appendix Table 3
Window for sacituzumab govitecan infusion for Cycle 1 Day 8 updated to match window for other infusion days.	Section 3.2.1 (Tables 6 and 7)
Timeframe between prior anticancer therapy and start of magrolimab updated.	Synopsis, Section 4.3

Rationale for Key Changes Included in Amendment 4	Affected Sections
Definition of uncontrolled hypercalcemia updated for clarity.	Synopsis, Section 4.3
Clarification was added regarding requirement of a new tumor biopsy at the time of rescreening for patients enrolled in Cohort 1 Arm B that rescreen to enroll in Cohort 2.	Section 6.9, Appendix Table 4
Requirements for collection prior to study drug initiation updated to align with current practice.	Section 7.3.1
Secondary efficacy endpoint analyses were updated in line with changes made in secondary objective and endpoints.	Section 8.5.2
Changes incorporated from Administrative Amendments 1 and 2 for Protocol Amendment 3.	Sections 6.2.2, 6.5 (Table 17), and 6.6, and Appendix Table 1
Minor changes to correct typographic errors.	Throughout, as needed

Separate tracked change (red-lined) documents comparing Amendment 3, Amendment 3.1-UK, and Amendment 3.2-KOR to this amendment may be made available upon the publication of this protocol.

Amendment 3.2-KOR (01 February 2023)

Rationale for Key Change Included in Amendment 3.2-KOR	Affected Sections
Patients in South Korea are not permitted to be transfused to meet the eligibility criteria for hemoglobin.	Synopsis, Sections 4.2, 4.3, and 7.8.1.2

Amendment 3.1-KOR (31 October 2022)

Rationale for Key Change Included in Amendment 3.1-KOR	Affected Sections
Correction of a typographical error in the synopsis, clarifying that the Safety Run-in Cohort 2 starting dose (after priming) is 60 mg/kg every 3 weeks.	Synopsis

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	31-Jan-2024 01:28:22