GILEAD

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Multi-Arm Study of Magrolimab in Patients With Solid Tumors
Plain Language Short Title:	Study of Magrolimab in Patients With Solid Tumors
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	117687
EudraCT Number:	2020-005265-14
Clinical Trials.gov Identifier:	NCT04827576
Indication:	Solid Tumors
Protocol ID:	GS-US-548-5918
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date Amendment History:	Amendment 5: 24 October 2023 Original: 15 December 2020 Amendment 1: 03 March 2021 Amendment 2: 15 March 2021 Amendment 3: 14 December 2021 Amendment 4: 27 January 2022 High-level summary of the history of amendments is provided in Appendix 10.
Country-specific Requirements:	Country-specific requirements, as applicable, are listed in Appendix 9.

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

CONFIDENTIALITY STATEMENT

The information contained in this document, particularly unpublished data, is the property or under control of Gilead Sciences, Inc., and is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable institutional review board or independent ethics committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Gilead Sciences, Inc., except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

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<tr><td>Study Centers Planned:</td><td>Approximately 50 centers globally</td></tr>
<tr><td>Objectives and Endpoints:</td><td>
<table>
<tr><th>Primary Objectives</th><th>Primary Endpoints</th></tr>
<tr><td>• To evaluate the safety, tolerability, and recommended Phase 2 dose of magrolimab + docetaxel combination therapy in solid tumors (Safety Run-in Cohort 1, Phase 2 Cohorts 1a, 1b, and 1c)
• To evaluate the efficacy of magrolimab + docetaxel combination therapy in solid tumors as determined by investigator-assessed objective response rate (ORR) (Phase 2 Cohorts 1a, 1b, and 1c)</td><td>• Incidence of adverse events (AEs) and laboratory abnormalities according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (Appendix 5; Safety Run-in Cohort 1, Phase 2 Cohorts 1a, 1b, and 1c)
• ORR, defined as the proportion of patients who achieve a complete response or partial response, as measured by Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, as determined by investigator assessment (Phase 2 Cohorts 1a, 1b, and 1c)</td></tr>
<tr><th>Secondary Objectives</th><th>Secondary Endpoints</th></tr>
<tr><td>• To evaluate progression-free survival (PFS) by investigator assessment (Phase 2 Cohorts 1a, 1b, and 1c)
• To evaluate additional measures of efficacy of magrolimab + docetaxel combination therapy, including duration of response (DOR) and overall survival (OS) (Phase 2 Cohorts 1a, 1b, and 1c)</td><td>• PFS from date of dose initiation as determined by investigator assessment per RECIST, Version 1.1 (Phase 2 Cohorts 1a, 1b, and 1c)
• DOR, defined as time from first documentation of complete response or partial response to the earliest date of documented disease progression, per RECIST, Version 1.1, or death from any cause, whichever occurs first, as</td></tr>
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</td></tr>
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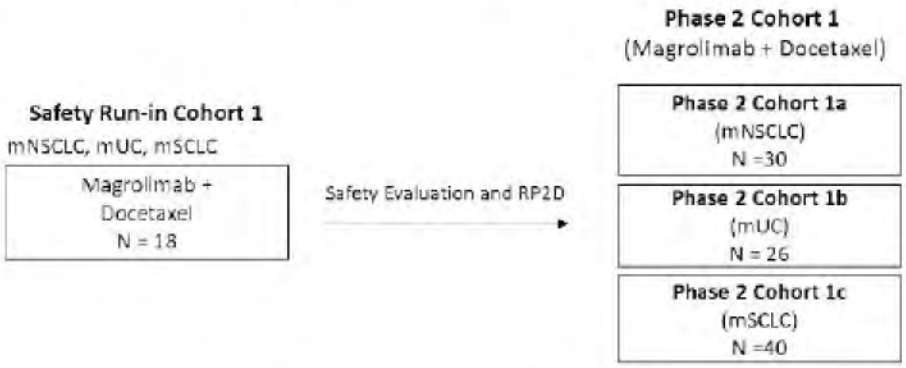
	• To evaluate the pharmacokinetics (PK) and immunogenicity of magrolimab when given with docetaxel as a combination therapy (Safety Run-in Cohort 1, Phase 2 Cohorts 1a, 1b, and 1c) determined by investigator assessment (Phase 2 Cohorts 1a, 1b, and 1c) • OS, defined as date of dose initiation (Phase 2 Cohorts 1a, 1b, and 1c) to death from any cause. • Magrolimab concentration versus time and antidrug antibodies to magrolimab (Safety Run-in Cohort 1; Phase 2 Cohorts 1a, 1b, and 1c)
	CCI
Study Design:	This Phase 2, open-label, multicenter, multi-arm study is evaluating magrolimab + docetaxel combination therapy for patients with solid tumors. This study will consist of the following Safety Run-in Cohort: • **Safety Run-in Cohort 1:** magrolimab + docetaxel combination in patients with solid tumors (metastatic non-small cell lung cancer [mNSCLC], metastatic urothelial cancer [mUC], and metastatic small cell lung cancer [mSCLC]) After completion of Safety Run-in Cohort 1, Phase 2 Cohort 1 will occur as follows: • **Phase 2 Cohort 1:** a cohort of patients with solid tumors (mNSCLC [Phase 2 Cohort 1a], mUC [Phase 2 Cohort 1b], and mSCLC [Phase 2 Cohort 1c]) The study schematic is provided below.  mNSCLC = metastatic non-small cell lung cancer; mSCLC = metastatic small cell lung cancer; mUC = metastatic urothelial cancer; RP2D = recommended Phase 2 dose

	Safety Run-in Cohort 1: A dose-limiting toxicity (DLT) evaluation period of 1 cycle (21 days) will occur. After 6 patients have completed the DLT evaluation period, a decision will be made on further expansion or dose de-escalation. 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 fewer of 6 DLT-evaluable patients experience a DLT in Cycle 1, enrollment into Phase 2 Cohort 1 will begin at this dose level as the recommended Phase 2 dose. • If more than 2 patients experience at least 1 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. Up to approximately 18 patients could be potentially enrolled and evaluated during the Safety Run-in Cohort. **DLT Assessment Period:** The DLT assessment period will be the first cycle (21 days) and applies to Safety Run-in Cohort 1. 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 1 dose of docetaxel in Safety Run-in Cohort 1. 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 Cohort 1 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 recommended dose for Phase 2 Cohort 1 is determined, the sponsor will open Phase 2 Cohort 1. Phase 2 Cohort 1 will treat up to 30 patients with mNSCLC (Phase 2 Cohort 1a), up to 26 patients with mUC (Phase 2 Cohort 1b), and up to 40 patients with mSCLC (Phase 2 Cohort 1c) to evaluate efficacy.
Number of Patients Planned:	Up to approximately 114 patients in total • Safety Run-in Cohort 1: up to approximately 18 patients • Phase 2 Cohort 1: up to approximately 96 patients

Target Population:	**Phase 2 Cohort 1:** Patients with mNSCLC, mUC, and mSCLC
Duration of Treatment:	Cycle lengths are 21 days for the Safety Run-in Cohort 1 and Phase 2 Cohort 1. 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, ≥ 18 years of age 4) Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. 5) Laboratory measurements, blood counts: a) Hemoglobin must be ≥ 9 g/dL prior to initial dose of study drug. NOTE: Transfusions are allowed to meet eligibility (see Section 7.8.1.1.1 in the clinical protocol and exclusion criterion 4) b) Absolute neutrophil count ≥ 1.5×10^9/L c) Platelets ≥ 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 × upper limit of normal (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 (See Section 7.8.1.1.1 in the clinical protocol)

	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 6. 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) Criterion removed. **Cohort-Specific Inclusion Criteria** Patients need to fulfill the following cohort-specific criteria, in addition to satisfying the inclusion criteria for all patients: 12) Criterion removed. 13) Criterion removed. 14) Safety Run-in Cohort 1: Patients with metastatic advanced solid tumors who have had at least 1 prior line of systemic anticancer therapy (mNSCLC and mSCLC) in a locally advanced/metastatic setting, or 2 prior lines of systemic anticancer therapy (mUC) in a locally advanced/metastatic setting, and not more than 3 prior lines of systemic anticancer therapy in a locally advanced/metastatic setting. 15) Phase 2 Cohort 1a (mNSCLC): Patients with NSCLC who have had treatment with platinum-based chemotherapy and immune checkpoint inhibitor therapy in a locally advanced/metastatic setting, either in combination or sequentially (unless not eligible for one of these therapies) are eligible. At least 1 prior line of systemic anticancer therapy in a locally advanced/metastatic setting is required and not more than 2 prior lines of systemic anticancer therapy in a locally advanced/metastatic setting are allowed. Patients treated with a taxane within 12 months or patients refractory to prior taxane treatment are excluded. Patients whose tumors have genomic alterations for which there are approved therapies (eg, EGFR, ROS1, ALK, NTRK, MET exon 14) are excluded. 16) Phase 2 Cohort 1b (mUC): Patients with UC who have had prior treatment with systemic chemotherapy and immune checkpoint inhibitor therapy in a locally advanced/metastatic setting (unless not eligible for one of these therapies) are eligible. At least 2 prior lines of systemic anticancer therapy in a locally advanced/metastatic setting are required and not more than 3 prior lines of systemic anticancer therapy in a locally advanced/metastatic setting are allowed. Patients treated with a taxane within 12 months or patients refractory to prior taxane treatment are excluded.

	17) Phase 2 Cohort 1c (mSCLC): Patients with SCLC who have had prior treatment with platinum-based chemotherapy with or without immunotherapy are eligible. At least 1 prior line of systemic anticancer therapy in a locally advanced/metastatic setting is required and not more than 2 prior lines of systemic anticancer therapy in a locally advanced/metastatic setting are allowed. Patients treated with a taxane within 12 months or patients refractory to prior taxane treatment are excluded. Note: Maintenance therapies are not counted as separate lines of therapy. **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 (radiation and/or surgery and/or other CNS-directed therapy who have not received corticosteroids for at least 4 weeks) are allowed. 4) Red blood cell (RBC) transfusion dependence, defined as requiring more than 2 units of packed red blood cell 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. 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 trial 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. 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 3 years.

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

13) Prior anticancer therapy including but not limited to chemotherapy, immunotherapy, or investigational agents within 4 weeks prior to magrolimab is not permitted.

NOTE: Palliative, localized, non-CNS radiotherapy to areas of non-target disease, previous hormonal therapy with luteinizing hormone releasing hormone agonists for prostate or breast cancer, and treatment with bisphosphonates and receptor activator of nuclear factor kappa B ligand (RANKL) inhibitors are not criteria for exclusion. There is no required minimum washout period for these therapies. Patients should be recovered from the effects of radiation.

Study Procedures/ Frequency:

In Safety Run-in Cohort 1, eligible patients will receive magrolimab + docetaxel. The study treatments are shown below.

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

Drug	Dose Level	Dosing (Cycles Are 21 Days)		
		Cycle 1	Cycle 2	Cycle 3+ (maintenance dosing)
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
Docetaxel	75 mg/m^2	75 mg/m^2 IV (1 h ± 5 min) on Day 1	75 mg/m^2 IV (1 h ± 5 min) on Day 1	75 mg/m^2 IV (1 h ± 5 min) on Day 1

IV = intravenous

<table>
<tr><td></td><td>

Phase 2 Cohort 1: Dose Level and Schedule

<table>
<tr><th rowspan="2">Drug</th><th rowspan="2">RP2D[a] Starting Dose</th><th colspan="3">Dose Schedule (Cycles Are 21 Days)</th></tr>
<tr><th>Cycle 1</th><th>Cycle 2</th><th>Cycle 3+ (maintenance dosing)</th></tr>
<tr><td rowspan="3">Magrolimab</td><td>30 mg/kg</td><td>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</td><td>30 mg/kg IV (2 h ± 30 min) on Days 1, 8, and 15</td><td>60 mg/kg IV (2 h ± 30 min) on Day 1</td></tr>
<tr><td>OR
20 mg/kg</td><td>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</td><td>20 mg/kg IV (2 h ± 30 min) on Days 1, 8, and 15</td><td>45 mg/kg IV (2 h ± 30 min) on Day 1</td></tr>
<tr><td>OR
15 mg/kg</td><td>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</td><td>15 mg/kg IV (2 h ± 30 min) on Days 1, 8, and 15</td><td>30 mg/kg IV (2 h ± 30 min) on Day 1</td></tr>
<tr><td>Docetaxel</td><td>75 mg/m^2 IV</td><td>75 mg/m^2 IV (1 h ± 5 min) on Day 1</td><td>75 mg/m^2 IV (1 h ± 5 min) on Day 1</td><td>75 mg/m^2 IV (1 h ± 5 min) on Day 1</td></tr>
</table>

IV = intravenous; RP2D = recommended Phase 2 dose
a RP2D as determined in Safety Run-in Cohort 1.

Cycle lengths are 21 days for Safety Run-in Cohort 1 and Phase 2 Cohort 1. Patients may continue treatment unless they develop unacceptable toxicity that cannot be clinically managed by dose or schedule modifications or if they have confirmed progressive disease according to RECIST, Version 1.1.

</td></tr>
<tr><td>**Test Product, Dose, and Mode of Administration:**</td><td>

<u>Safety Run-in Cohort 1 Doses:</u>

- Magrolimab 1 mg/kg IV (priming)
- Magrolimab 30 mg/kg IV
- Magrolimab 60 mg/kg IV

In combination with docetaxel 75 mg/m^2 IV

<u>Phase 2 Cohort 1:</u>

Magrolimab dose will be determined in Safety Run-in Cohort 1.

</td></tr>
<tr><td>**Reference Therapy, Dose, and Mode of Administration:**</td><td>Not applicable</td></tr>
</table>

Criteria for Evaluation:	
Safety:	Safety will be evaluated by data including the incidence of adverse events (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:	Efficacy will be evaluated by PFS, ORR, DOR, and OS. Assessment of response will be measured by RECIST, Version 1.1 as determined by investigator assessment.
Pharmacokinetics:	Magrolimab serum drug concentrations will be assessed at predose at multiple time points until study discontinuation. Peripheral blood for immunogenicity assessments for antidrug antibodies 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 evaluable 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 1 dose of docetaxel in Safety Run-in Cohort 1 For Safety Run-in Cohort 1, the modified Intent-to-Treat (ITT) and Safety Analysis Sets will include all patients who received at least 1 dose of any study drug. For Phase 2 Cohort 1, the modified ITT Analysis Set and the Safety Analysis Set will include all patients who received at least 1 dose of any study drug. 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, 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 required dosing cycles (21 days) and the follow-up 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.

Efficacy Analysis

For Phase 2 Cohort 1, ORR along with the 95% CI based on the Clopper-Pearson method will be estimated for each cohort (Phase 2 Cohorts 1a, 1b, and 1c). 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

For Phase 2 Cohort 1, a sample size of 30 patients in the mNSCLC cohort and 40 patients for mSCLC cohort were calculated using one sample proportion test. The sample size of 26 patients for the mUC cohort was calculated using exact method instead of one sample test due to smaller sample size.

Tumor Type	Sample Size	Null ORR	Alternative ORR	1-sided alpha	Power
mNSCLC	30	13%	25%	0.2	81%
mUC	26	12.4%	28%	0.1	78%
mSCLC	40	9%	20%	0.15	84%

The null ORR for each of the respective tumor cohorts are based on historical taxane efficacy data in the second line setting. Power calculations were performed using EAST 6.5 and nQuery 8.0.

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

ABO	any of the 4 blood groups A, B, AB, and O comprising the ABO system
ADA	antidrug antibody
ADC	antibody-drug conjugate
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
CD47	cluster of differentiation 47
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRO	contract/clinical research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450 enzyme
DAT	direct antiglobulin test
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EC	ethic committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EOT	end of treatment
EU	European Union
Fc	fragment crystallizable
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Gilead	Gilead Sciences

HR	hazard ratio
HU	hydroxyurea
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
LHRH	luteinizing hormone releasing hormone
mAb	monoclonal antibody
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mNSCLC	metastatic non-small cell lung cancer
MOA	mechanism of action
mSCLC	metastatic small cell lung cancer
MTD	maximum tolerated dose
mUC	metastatic urothelial cancer
nab	nanoparticle albumin-bound
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PS	Patient Safety
RANKL	receptor activator of nuclear factor kappa B ligand
RBC	red blood cell

RECIST	Response Evaluation Criteria in Solid Tumors
Rh	rhesus
RNA	ribonucleic acid
RO	receptor occupancy
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SCLC	small cell lung cancer
SIRPα	signal regulatory protein alpha
SmPC	summary of product characteristics
SOP	standard operating procedure
SRT	safety review team
SSRs	special situation reports
SUSAR	suspected unexpected serious adverse reaction
TCR	T cell receptor
UC	urothelial cancer
ULN	upper limit of normal
US	United States
USPI	United States prescribing information
w/v	weight-to-volume ratio
WES	whole exome sequencing

1. INTRODUCTION

1.1. Background

1.1.1. Background on Relapsed/Refractory Solid Tumors Including Metastatic Non-Small Cell Lung Cancer, Metastatic Urothelial Cancer, and Metastatic Small Cell Lung Cancer

For many solid tumors, immune checkpoint inhibitors, specifically anti–programmed cell death protein 1 (PD-1) and anti–programmed cell death ligand-1 (PD-L1) antibodies, have dramatically improved the treatment outcomes for patients. Several T-cell checkpoint inhibitors are United States (US) Food and Drug Administration (FDA) approved for multiple solid tumors including pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, and cemiplimab. For most tumor types, standard of care for frontline treatment consists of combination chemotherapy, immune checkpoint inhibitors, or the combination. However, once patients fail standard chemotherapy and/or immune checkpoint inhibitors, treatment options are generally more limited. Often, single-agent chemotherapy is standard of care in this setting. Efficacy is limited in this setting with observed objective response rates (ORRs) around 10% for most single-agent chemotherapeutic regimens. Thus, novel agents that can safely combine and enhance efficacy of these chemotherapies are needed to improve treatment outcomes in this setting. This study will initially evaluate magrolimab combination with chemotherapy in multiple solid tumors including metastatic non–small cell lung cancer (mNSCLC), metastatic urothelial cancer (mUC), and metastatic small cell lung cancer (mSCLC).

1.1.1.1. NSCLC Background

Lung cancer is the leading cause of cancer-related mortality. Approximately 80% to 85% of all lung cancers are NSCLC. Recent advances with immune checkpoint inhibitor therapy have dramatically improved the prognosis of lung cancer and these immune checkpoint inhibitor therapies, as monotherapy or in combination, are mainly used in the frontline metastatic setting. However, after failure of immune checkpoint inhibitor therapy and/or frontline chemotherapy, there are limited treatment options for the majority of patients. According to National Comprehensive Cancer Network (NCCN) guidelines, the use of single-agent chemotherapy (including taxanes) is the standard of care for patients with recurrent or metastatic NSCLC after failure of platinum-based therapy and/or immune checkpoint therapy {Ettinger 2019}. The main options for single-agent chemotherapy in this setting generally include docetaxel (with or without ramucirumab), erlotinib, and pemetrexed. Historical median progression-free survival (PFS) rates in second-line NSCLC treated with single-agent chemotherapy is approximately 3 months with a median survival of approximately 6 to 8 months {Shepherd 2000}. Thus, novel agents that can safely combine with single-agent chemotherapy and improve clinical efficacy are needed.

1.1.1.2. SCLC Background

Small cell lung cancer is a neuroendocrine tumor that represents approximately 15% of all lung cancers. Small cell lung cancer predominantly occurs in smokers and is distinguished from other NSCLC types by its rapid proliferation rate, early development of metastases, and initial presentation with disseminated disease. While patients with SCLC tend to initially present with metastatic disease, SCLC is highly responsive to chemotherapeutic agents (with and without radiation), which are the mainstay of frontline treatment. Frontline chemotherapy generally consists of platinum-based combinations (ie, platinum + etoposide). Median overall survival (OS) with platinum-based chemotherapies in the frontline metastatic setting is approximately 9 to 10 months {Rossi 2012}. Recently, the addition of immune checkpoint inhibitors to frontline platinum-based chemotherapy combinations have demonstrated improvement in clinical outcomes leading to FDA approval of checkpoint inhibitors (atezolizumab and durvalumab) in the frontline metastatic disease population. In a randomized Phase 3 study, atezolizumab in combination with carboplatin and etoposide demonstrated a statistically significant improvement in PFS compared to carboplatin + etoposide (12.3 vs 10.3 months, hazard ratio [HR] = 0.70) with a similar toxicity profile across both groups {Horn 2018}. In another Phase 3 study, durvalumab in combination with platinum-etoposide led to an improvement in OS compared to chemotherapy control (12.9 vs 10.5 months, HR = 0.75) {Paz-Ares 2019}. Thus, the addition of immune checkpoint inhibitors to chemotherapy has led to moderate improvements to patient outcomes in the frontline metastatic setting. For patients who fail frontline chemotherapy with or without an immune checkpoint inhibitor, there are limited treatment options, with single-agent chemotherapy as the main standard of care. The median OS in this advanced later line setting is approximately 6 months {Smit 1998, Yamamoto 2006}. Novel treatment options or combinations in the advanced later line setting are needed to improve outcomes.

1.1.1.3. UC Background

Bladder cancer is the most common malignancy involving the urinary system. Urothelial carcinoma is the predominant histologic type in the US and Europe, accounting for over 90% of all bladder cancers. Systemic chemotherapy is the standard approach for the initial treatment of patients with inoperable locally advanced or metastatic urothelial cancer (UC). Although initial response rates are high, the median OS with combination chemotherapy (primarily cisplatin-based) is approximately 15 months {von der Maase 2000}. Recently, immune checkpoint inhibitor therapies (notably pembrolizumab and atezolizumab) have moved into the frontline setting, particularly for those who are ineligible for cisplatin therapy. This usage is primarily based on Phase 2 studies demonstrating a 29% ORR, median duration of response (DOR) of 30 months, and median OS of 11.3 months for pembrolizumab {Vuky 2020}. Similar efficacy data have been observed with atezolizumab {Balar 2017}. Immune checkpoint therapy in combination with chemotherapy is being evaluated in the frontline metastatic setting. In addition to frontline patients who are ineligible for cisplatin-based chemotherapy, immune checkpoint therapy is primarily used in patients who fail frontline chemotherapy. Multiple immune checkpoint inhibitors are approved in this setting based on either Phase 2 or randomized Phase 3 data based on either encouraging durable response rates or improvement in PFS compared to chemotherapy standard of care. Lastly, a novel modality of antibody-drug conjugates (ADCs) have also recently demonstrated benefit in UC. Enfortumab vedotin, a nectin-4 ADC, was approved in 2019 for the treatment of locally

advanced or metastatic UC in patients who previously received an anti-PD-1/L1 inhibitor and a platinum-containing chemotherapy regimen. This approval was based on a Phase 2 study demonstrating an ORR of 44% with a median PFS of 6 months. In summary, recent treatment advances including immune checkpoint inhibitors and ADCs have improved the treatment outcomes in patients with mUC. However, patients in the advanced later line setting, especially after 2 lines of therapy, have limited treatment options and require more effective therapies. Currently, atezolizumab is being investigated in combination with magrolimab in mUC (NCT ID# 03869190).

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 fragment crystallizable (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 per the 2020 investigator's brochure (IB), magrolimab is being investigated as an anticancer therapeutic in 6 ongoing clinical studies in the 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 per the data cut-off dates in the 2020 IB.

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. As such, 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 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 (HU) had no effect on magrolimab-induced phagocytosis, nor did HU 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 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 monkey.

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 non–severely 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 in house, but all the available data (literature, data from knockout mice, and limited clinical data) suggest no role for CD47 on embryo-fetal development.

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 tumor. In this study, patients were treated with weekly magrolimab doses ranged 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), similar to 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 of magrolimab 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

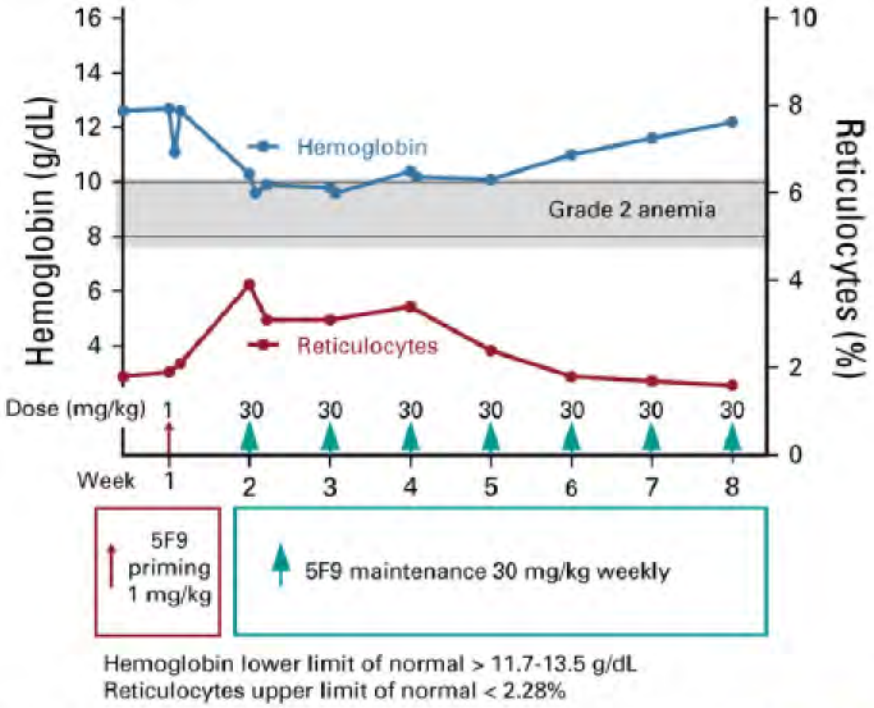
Magrolimab is administered as an IV infusion and it is currently being studied in 6 clinical studies. Two completed single-agent Phase 1 studies include Study SCI-CD47-001 in patients with advanced solid tumors and lymphomas, and Study SCI-CD47-002 in patients with advanced later line AML, along with 2 Phase 1b partnered studies in AML as well as UC. Four combination studies include the following: Study 5F9003, a Phase 1b/2 study of magrolimab with rituximab in patients with advanced later line NHL; Study 5F9004, a Phase 1b/2 study of magrolimab with cetuximab in patients with solid tumor 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 tumor 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 improving their hemoglobin 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 per 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 occurred in 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) is indicative of 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**



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 5.6 and 7.8.1.2. 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 a Phase 1b/2 study of magrolimab in combination with cetuximab in advanced later line CRC patients (Study 5F9004), 2 objective responses out of 32 patients (6%) were observed in advanced later line 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 advanced later line NHL were treated with magrolimab in combination with rituximab. In 97 NHL patients evaluable for efficacy that included diffuse large B-cell lymphoma (DLBCL) and indolent lymphoma, the ORR was 45% with a complete response (CR) 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 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 Docetaxel

1.3.1. Description of Docetaxel

Docetaxel (Taxotere) is an anticancer chemotherapy drug classified as an anti-microtubule inhibitor and taxane. Docetaxel is indicated for multiple solid tumors as a single agent {Taxotere® 1995, Taxotere® 1996}.

1.3.2. Clinical Data for Docetaxel

Docetaxel is approved for use as monotherapy in multiple solid tumors including NSCLC, head and neck squamous cell carcinoma, breast cancer, hormone refractory prostate cancer, and gastric adenocarcinoma. Docetaxel is also widely used as standard of care in multiple solid tumors, including mUC and mSCLC, who fail frontline chemotherapy and/or immune checkpoint therapy {Taxotere® 1995, Taxotere® 1996}.

The most common AEs across all docetaxel indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia {Taxotere® 1995, Taxotere® 1996}. Docetaxel is contraindicated in patients with neutrophil counts less than 1500 cells/mm^3 and in patients with hypersensitivity to docetaxel or polysorbate 80. Docetaxel carries a black box warning for toxic deaths, hepatotoxicity, neutropenia, hypersensitivity reactions, and fluid retention. In addition, cutaneous reactions, severe skin toxicity, neurologic reactions (including paresthesia, dysesthesia, and pain), asthenia, and potential fetal harm have been observed with docetaxel.

Docetaxel is standard of care as monotherapy for advanced later line patients in multiple solid tumor types including mNSCLC, mUC, and mSCLC, indications studied in this protocol. In general the efficacy observed with docetaxel monotherapy in these tumor types in patients who fail standard chemotherapy, immune checkpoint inhibitor, or the combination results in an ORR of approximately 10% (ranging from 9% to 13% in SCLC, UC, and NSCLC) {Bellmunt 2017, Rittmeyer 2017, Smit 1998}. Median PFS ranges from approximately 3 to 5 months in these indications.

In summary, docetaxel is used as a standard-of-care option for second and later lines of therapy for multiple solid tumor types after frontline chemotherapy and/or immune checkpoint therapy.

1.4. Information About Auxiliary Medicinal Products

Acetaminophen (also known as paracetamol), diphenhydramine, and dexamethasone are considered auxiliary medicinal products (AxMPs) for this clinical study (Appendix 2). Acetaminophen is approved for pain relief and fever reduction. Diphenhydramine is an antihistamine and is approved for amelioration of allergic reactions. Dexamethasone is an anti-inflammatory medication and is used for the amelioration of allergic reactions. The use of these medications in this study is described in Sections 5.6 and 7.8.1.2.

Additional details on acetaminophen, diphenhydramine, and dexamethasone can be found in the prescribing information.

1.5. Rationale for This Study

Strong nonclinical and clinical rationale exists for combining magrolimab with chemotherapy agents, including taxanes. First, chemotherapeutic agents have been demonstrated to enhance prophagocytic signals on tumor cells that 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 advanced later line 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 1.2.3.2).

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

Standard-of-care therapy for many newly diagnosed metastatic solid tumor cancers include a platinum-based chemotherapeutic agent and immune checkpoint inhibitor (ie, anti-PD-1/PD-L1 antibodies) where applicable. Encouraging clinical activity has been seen specifically with immune checkpoint inhibitors as monotherapy or in combination with chemotherapy in the frontline setting and has dramatically improved response rates, PFS, and OS. However, patients with solid tumors who fail frontline chemotherapeutic regimens and/or immune checkpoint inhibitors have a poor prognosis with generally limited treatment options. For the most part, single-agent or combination chemotherapy represents the major standard care option in the advanced later line metastatic setting. For many solid tumors (including the solid tumor types evaluated in this study), taxanes represent the predominant standard-of-care chemotherapy option post-platinum/immune checkpoint inhibitor therapy. While taxanes are mainly used in these indications postplatinum-based chemotherapy and/or immune checkpoint inhibitor therapy, the clinical activity is modest. Specifically, the ORRs in SCLC, UC, and NSCLC range from 9%, 12.4%, and 13%, respectively {Bellmunt 2017, Rittmeyer 2017, Smit 1998}. Median PFS in these tumor types in this line of therapy is approximately 3 to 5 months. These populations therefore represent a high unmet medical need. Novel regimens, especially those that can safely and effectively combine with chemotherapy, are needed to increase clinical benefit.

The strong nonclinical and clinical data support the evaluation of magrolimab in combination with chemotherapy, including taxanes, in patients with advanced later line solid tumors.

One of the objectives of this Phase 2 study cohort is to evaluate the safety, tolerability, and recommended Phase 2 dose of magrolimab in combination with docetaxel in solid tumors. In Phase 2 Cohort 1, NSCLC, SCLC, and UC will be specifically evaluated for efficacy given that taxanes represent the predominant standard-of-care chemotherapy option in these tumor types. Docetaxel was specifically chosen given its high usage pattern within taxanes in the US and Europe as well as the lack of anticipated overlapping toxicities.

In summary, strong nonclinical and clinical rationale exists for evaluating a combination of magrolimab and docetaxel in solid tumor malignancies.

1.6. Rationale for Dose Selection of Magrolimab

The rationale for the magrolimab dose proposed in this study originates from safety, efficacy, and PK/pharmacodynamic (PD) data, and modelling 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}.

In addition, in solid tumors where the combination therapy (chemotherapy or pembrolizumab) 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. 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 modelling 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.

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

The following magrolimab dosing regimen is proposed for Safety Run-in Cohort 1 and Phase 2 Cohort 1 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 every cycle on Day 1

1.7. 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 safely combine with chemotherapy to enhance efficacy are needed in this high unmet need patient setting.

Magrolimab can eliminate tumor cells through macrophage-mediated phagocytosis. Magrolimab activity can be enhanced with chemotherapeutic agents that can increase prophagocytic signals on tumors cells, leading to synergistic phagocytosis. Nonclinical data have shown that magrolimab in combination with taxanes lead 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 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 docetaxel.

Treatment with the proposed combination of magrolimab and docetaxel for solid tumors is not anticipated to pose a significantly increased risk to patients enrolled in this trial compared to the risk of treatment with either agent alone. Based on the clinical profiles of magrolimab and docetaxel, overlapping toxicities (except for potential anemia) are not anticipated with the combination. While magrolimab does cause a transient, generally mild to moderate anemia, docetaxel 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. In addition to anemia, neutropenia, thrombocytopenia, and infections have been reported in patients treated with magrolimab. Specific clinical and laboratory monitoring of magrolimab- and docetaxel-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.

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 4 for further details on the risks and risk mitigation strategy.

In summary, based on 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 docetaxel in patients with solid tumors is anticipated to have an acceptable risk-benefit ratio to the patients enrolled in this study.

1.8. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), 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. GS-US-548-5918: Study Objectives and Endpoints

Primary Objectives	Primary Endpoints
• To evaluate the safety, tolerability, and recommended Phase 2 dose of magrolimab + docetaxel combination therapy in solid tumors (Safety Run-in Cohort 1, Phase 2 Cohorts 1a, 1b, and 1c) • To evaluate the efficacy of magrolimab + docetaxel combination therapy in solid tumors as determined by investigator-assessed objective response rate (ORR) (Phase 2 Cohorts 1a, 1b, and 1c)	• Incidence of adverse events (AEs) and laboratory abnormalities according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (Appendix 5; Safety Run-in Cohort 1, Phase 2 Cohorts 1a, 1b, and 1c) • ORR, defined as the proportion of patients who achieve a complete response or partial response, as measured by Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, as determined by investigator assessment (Phase 2 Cohorts 1a, 1b, and 1c)
Secondary Objectives	**Secondary Endpoints**
• To evaluate progression-free survival (PFS) by investigator assessment (Phase 2 Cohorts 1a, 1b, and 1c) • To evaluate additional measures of efficacy of magrolimab + docetaxel combination therapy, including duration of response (DOR) and overall survival (OS) (Phase 2 Cohorts 1a, 1b, and 1c) • To evaluate the PK and immunogenicity of magrolimab when given with docetaxel as a combination therapy (Safety Run-in Cohort 1, Phase 2 Cohorts 1a, 1b, and 1c)	• PFS from date of dose initiation as determined by investigator assessment per RECIST, Version 1.1 (Phase 2 Cohorts 1a, 1b, and 1c) • DOR, defined as time from first documentation of complete response or partial response to the earliest date of documented disease progression, per RECIST, Version 1.1, or death from any cause, whichever occurs first, as determined by investigator assessment (Phase 2 Cohorts 1a, 1b, and 1c) • OS, defined as date of dose initiation (Phase 2 Cohorts 1a, 1b, and 1c) to death from any cause. • Magrolimab concentration versus time and antidrug antibodies to magrolimab (Safety Run-in Cohort 1; Phase 2 Cohorts 1a, 1b, and 1c)

3. STUDY DESIGN

3.1. Study Design

This Phase 2, open-label, multicenter, multiarm study is evaluating magrolimab + docetaxel combination therapy for patients with solid tumors. This study will consist of the following Safety Run-in Cohort:

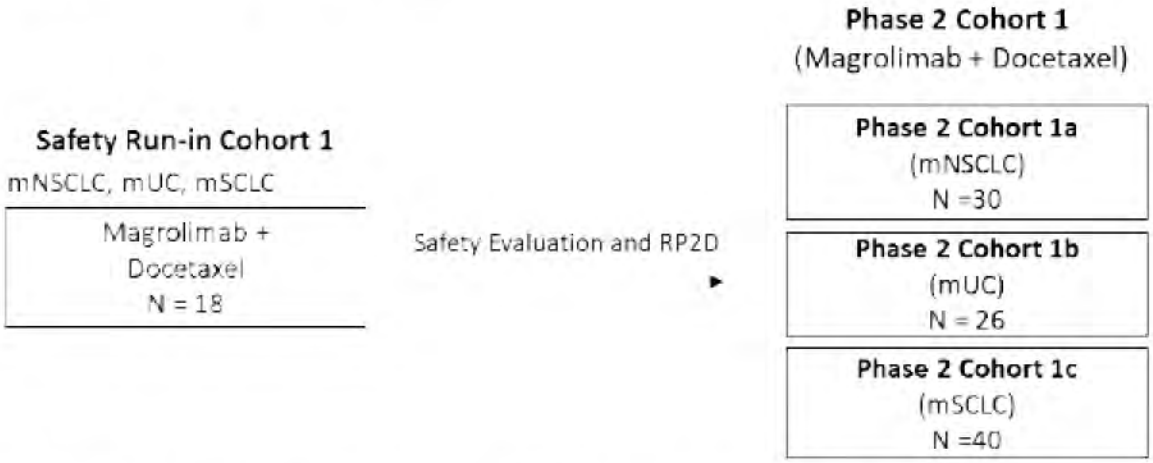
- **Safety Run-in Cohort 1:** magrolimab + docetaxel combination in patients with solid tumors (mNSCLC, mUC, and mSCLC)

After completion of Safety Run-in Cohort 1, Phase 2 Cohort 1 will occur as described in Section 3.1.2.

Patient participation will include screening, treatment, and follow-up. Screening will last up to 30 days before first dose of study treatment, during which time the patient's eligibility and baseline characteristics will be determined. Patients will receive study treatment per the dose schedule in Appendix Table 1.

The study schematic is presented in Figure 2.

Figure 2. Study Schema



mNSCLC = metastatic non–small cell lung cancer; mSCLC = metastatic small cell lung cancer; mUC = metastatic urothelial cancer; RP2D = recommended Phase 2 dose

3.1.1. Safety Run-in Cohort 1

A dose-limiting toxicity (DLT) evaluation period of 1 cycle (21 days) will occur. After 6 patients have completed the DLT evaluation period, decision will be made on further expansion or dose de-escalation.

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 as specified below.

Dose de-escalation decisions will be made as follows:

- If 2 or fewer of 6 DLT-evaluable patients experience a DLT in Cycle 1, enrollment into Phase 2 Cohort 1 will begin at this dose level as the recommended Phase 2 dose.
- If more than 2 patients experience at least 1 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.

Up to approximately 18 patients could be potentially enrolled and evaluated during Safety Run-in Cohort 1.

Dose de-escalation for Safety Run-in Cohort 1 is presented in Table 2. Based on the totality of the data, alternative doses of magrolimab not described in Table 2 may be considered for dose de-escalation by the Safety Review Team (SRT) and sponsor.

3.1.1.1. DLT Assessment Period

The DLT assessment period will be the first cycle (21 days) and applies to Safety Run-in Cohort 1. 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 1 dose of docetaxel in Safety Run-in Cohort 1.

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 Safety Run-in Cohort 1 will be replaced.

3.1.1.2. DLT Definition

All toxicities will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (Appendix 5).

A DLT is defined as any:

- Grade 3 or higher hematologic toxicity.
- 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.

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, requiring hospitalization or prolongation of existing hospitalization, disabling, or limiting self-care activities of daily living is considered a DLT.
- 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 14 days.
- Grade 3 indirect/unconjugated hyperbilirubinemia that resolves to ≤ Grade 2 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 baseline within < 72 hours, are not clinically complicated, and resolve spontaneously or respond to conventional medical interventions.
- Grade 3 elevation in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase that resolves to ≤ Grade 2 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 within 72 hours with adequate antiemetic and other supportive care.
- Grade 3 fatigue that resolves to ≤ Grade 2 within 1 week on study.
- Grade 3 magrolimab and docetaxel infusion reactions in the absence of an optimal pretreatment regimen, which is defined as acetaminophen or a comparable nonsteroidal anti-inflammatory agent, plus an antihistamine and corticosteroids.
- Grade 3 tumor lysis syndrome or electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia) that resolve to ≤ Grade 2 or baseline within 72 hours.

- Grade 3 or 4 lymphopenia or leukopenia not associated with other clinically significant consequences.

- Transient (≤ 48 hours) Grade 3 local reactions, flu-like symptoms, myalgias, fever, headache, acute pain, or skin toxicity that resolves to ≤ Grade 2 within 72 hours after medical management (eg, supportive care, including immunosuppressant treatment) has been initiated.

The recommended dose for Phase 2 Cohort 1 will be determined by the sponsor based on all relevant clinical and PK data (additional data such as biomarkers may also be considered) 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 in various cohorts.

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 Cohort 1

After completion of the Safety Run-in Cohort, Phase 2 Cohort 1 will occur as follows:

- **Phase 2 Cohort 1:** a cohort of patients with solid tumors (mNSCLC [Phase 2 Cohort 1a], mUC [Phase 2 Cohort 1b], and mSCLC [Phase 2 Cohort 1c]).

Once Safety Run-in Cohort 1 is completed and the recommended dose for Phase 2 Cohort 1 is determined, the sponsor will open Phase 2 Cohort 1. Phase 2 Cohort 1 will treat up to 30 patients with mNSCLC (Phase 2 Cohort 1a), up to 26 patients with mUC (Phase 2 Cohort 1b), and up to 40 patients with mSCLC (Phase 2 Cohort 1c) to evaluate efficacy.

3.2. Study Treatments

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

Table 2 shows the study treatments for Safety Run-in Cohort 1 and Table 3 shows the study treatments for Phase 2 Cohort 1. The schedules of assessment are provided in Appendix 3.

Table 2. Safety Run-in Cohort 1: Dose Level, Schedule, and De-escalation

Drug	Dose Level	Dosing (Cycles Are 21 Days)		
		Cycle 1	Cycle 2	Cycle 3+ (maintenance dosing)
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
Docetaxel	75 mg/m^2	75 mg/m^2 IV (1 h ± 5 min) on Day 1	75 mg/m^2 IV (1 h ± 5 min) on Day 1	75 mg/m^2 IV (1 h ± 5 min) on Day 1

IV = intravenous

Table 3. Phase 2 Cohort 1: Dose Level and Schedule

Drug	RP2D[a] Starting Dose	Dosing (Cycles Are 21 Days)		
		Cycle 1	Cycle 2	Cycle 3+ (maintenance dosing)
Magrolimab	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
	OR 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
	OR 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
Docetaxel	75 mg/m^2 IV	75 mg/m^2 IV (1 h ± 5 min) on Day 1	75 mg/m^2 IV (1 h ± 5 min) on Day 1	75 mg/m^2 IV (1 h ± 5 min) on Day 1

IV = intravenous; RP2D = recommended Phase 2 dose
a RP2D as determined in Safety Run-in Cohort 1.

3.3. Duration of Treatment

Cycle lengths are 21 days for Safety Run-in Cohort 1 and Phase 2 Cohort 1. Patients may continue treatment unless they develop unacceptable toxicity that cannot be clinically managed by dose or schedule modifications or if they have confirmed progressive disease according to RECIST, Version 1.1. Patients are not required to discontinue study drugs for disease progression per RECIST criteria, given the observation that delayed clinical benefit can occur with immune therapies beyond initial disease progression. Magrolimab can be continued if the combination partner drug (ie, docetaxel) is discontinued for unacceptable toxicity. Combination partner drug can be continued if magrolimab is discontinued for unacceptable toxicity. Study drug treatment may continue past the initial determination of disease progression according to RECIST, Version 1.1 if the following criteria are met:

- No new symptoms or worsening of previous symptoms
- Tolerance of magrolimab and docetaxel
- 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, central nervous 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 re-consent 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 by RECIST, Version 1.1 (treatment beyond disease progression by RECIST, Version 1.1 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 or other AEs)
- 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

Although disease progression is considered a sufficient reason for discontinuing a patient from study treatment, given the delayed treatment benefit commonly seen in immune therapies, the investigator is advised to continue to treat the patient until the confirmation of disease progression through a subsequent response assessment at least 4 weeks apart (ie, disease worsening compared to the previous assessment), or until the investigator considers the study treatment to be no longer clinically beneficial to the patient, or the change of disease state renders the patient unacceptable for further treatment in the judgment of the investigator. Patients may continue study drug treatment beyond RECIST, Version 1.1 disease progression as per 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 2.

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 selected 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, 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 schedules of assessments (Appendix Table 3).

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. Pharmacokinetics/Biomarker Samples for CCI

In addition to the study-specific informed consent 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 biomarker and PK specimens for CCI, in accordance with applicable regulations.

The remainder of their already collected specimens for CCI may be used to advance development of the drug and/or increase our knowledge and understanding of the biology of the disease under investigation and related diseases. These specimens may also be used to study the association of biomarkers with biological pathways, disease pathogenesis, progression and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. In addition, these specimens may be used to develop biomarker and/or diagnostic assays and establish the performance characteristics of these assays. The analysis of CCI specimens may facilitate the design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients CCI

Blood samples will be collected to measure biomarkers which may include but not be limited to the times points specified in the schedules of assessments (Appendix Table 3).

The already collected specimens for CCI will be destroyed no later than 15 years after the end of study or per country requirements.

4. PATIENT POPULATION

4.1. Number of Patients and Patient Selection

Up to approximately 114 patients may be enrolled in the study, with up to approximately 18 patients in Safety Run-in Cohort 1 and up to approximately 96 patients in Phase 2 Cohort 1.

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.

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, ≥ 18 years of age

4) Patients must have an ECOG performance status of ≤ 2.

5) Laboratory measurements, blood counts:

   a) Hemoglobin must be ≥ 9 g/dL prior to initial dose of study drug. NOTE: Transfusions are allowed to meet eligibility (see Section 7.8.1.1.1 and exclusion criterion 4).

   b) Absolute neutrophil count (ANC) ≥ 1.5×10^9/L

   c) Platelets ≥ 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 × upper limit of normal (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 (see Section 7.8.1.1.1)

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 6.

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) Criterion removed.

Cohort-Specific Inclusion Criteria

Patients need to fulfill the following cohort-specific criteria, in addition to satisfying the inclusion criteria for all patients:

12) Criterion removed.

13) Criterion removed.

14) Safety Run-in Cohort 1: Patients with metastatic advanced solid tumors who have had at least 1 prior line of systemic anticancer therapy (mNSCLC and mSCLC) in a locally advanced/metastatic setting, or 2 prior lines of systemic anticancer therapy (mUC) in a locally advanced/metastatic setting, and not more than 3 prior lines of systemic anticancer therapy in a locally advanced/metastatic setting.

15) Phase 2 Cohort 1a (mNSCLC): Patients with NSCLC who have had treatment with platinum -based chemotherapy and immune checkpoint inhibitor therapy in a locally advanced/metastatic setting, either in combination or sequentially (unless not eligible for one of these therapies) are eligible. At least 1 prior line of systemic anticancer therapy in a locally advanced/metastatic setting is required and not more than 2 prior lines of systemic anticancer therapy in a locally advanced/metastatic setting are allowed. Patients treated with a taxane within 12 months or patients refractory to prior taxane treatment are excluded. Patients whose tumors have genomic alterations for which there are approved therapies (eg, EGFR, ROS1, ALK, NTRK, MET exon 14) are excluded.

16) Phase 2 Cohort 1b (mUC): Patients with UC who have had prior treatment with systemic chemotherapy and immune checkpoint inhibitor therapy in a locally advanced/metastatic setting (unless not eligible for one of these therapies) are eligible. At least 2 prior lines of systemic anticancer therapy in a locally advanced/metastatic setting are required and not more than 3 prior lines of systemic anticancer therapy in a locally advanced/metastatic setting are allowed. Patients treated with a taxane within 12 months or patients refractory to prior taxane treatment are excluded.

17) Phase 2 Cohort 1c (mSCLC): Patients with SCLC who have had prior treatment with platinum-based chemotherapy with or without immunotherapy are eligible. At least 1 prior line of systemic anticancer therapy in a locally advanced/metastatic setting is required and not more than 2 prior lines of systemic anticancer therapy in a locally advanced/metastatic setting are allowed. Patients treated with a taxane within 12 months or patients refractory to prior taxane treatment are excluded.

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

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 (radiation and/or surgery and/or other CNS-directed therapy who are off corticosteroids for at least 4 weeks) are allowed.

4) Red blood cell 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.

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 SIRPα-targeting agents

8) Current participation in another interventional clinical study

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.

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 3 years

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

13) Prior anticancer therapy including but not limited to chemotherapy, immunotherapy, or investigational agents within 4 weeks prior to magrolimab is not permitted.

NOTE: Palliative, localized, non-CNS radiotherapy to areas of nontarget disease, previous hormonal therapy with luteinizing hormone releasing hormone (LHRH) agonists for prostate or breast cancer, and treatment with bisphosphonates and receptor activator of nuclear factor kappa B ligand (RANKL) inhibitors are not criteria for exclusion. There is no required minimum washout period for these therapies. 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

Randomization will not be performed in this study.

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 to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, European Union (EU) Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), 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 Docetaxel

5.3.1. Formulation

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

5.3.2. Packaging and Labeling

Commercial product of docetaxel will be used for this study. Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice – 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

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

5.4. Dosage and Administration of Magrolimab

Vital signs will be assessed prior to any IV study drug administration.

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 > 10% change in weight from baseline. Modifications to the study drug doses administered should be made for a > 10% change in body weight and/or according to local and regional prescribing standards. Dose modifications for changes in body weight < 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. All patients should be monitored hourly during infusion. Patients should be monitored (including measurement of vital signs, as clinically appropriate) for signs and symptoms of IRRs, which have been observed in previous magrolimab studies.

Magrolimab doses will be given weekly during Cycles 1 and 2. Magrolimab is then administered every 3 weeks during Cycle 3 and beyond for a 21-day cycle. **Magrolimab doses are not to be given on consecutive days**.

When magrolimab is given in combination with docetaxel (Safety Run-in Cohort 1 and Phase 2 Cohort 1), magrolimab will be infused first. All patients will be monitored for 1 hour postinfusion for priming, repriming, and maintenance doses during Cycle 1. Postinfusion monitoring should begin after the infusion is complete but prior to administering docetaxel.

Postinfusion monitoring is not required for doses after Cycle 1. Patients who experience any treatment-emergent AEs during the observation period should be further monitored, as clinically appropriate. Refer to Section 7.8.1.1.2 for postinfusion hemoglobin reporting requirements.

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).

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 is provided in Section 5.5.

The magrolimab dosing regimens for each cohort are described in Table 2 and Table 3.

5.5. Dose Modifications and Delays for Magrolimab

The dose of magrolimab should not be reduced except in Safety Run-in Cohort 1 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/modification may be allowed in certain AEs/circumstances that must be approved by the sponsor. If a dose reduction is considered, an initial approximately 33% dose reduction from the recommended Phase 2 dose should be done (eg, from 30 mg/kg to 20 mg/kg and from 20 mg/kg to 15 mg/kg).

When docetaxel is delayed due to toxicities, magrolimab should continue independently as per the 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 10 to 20 days, the subsequent magrolimab dose may be administered earlier than scheduled in order to synchronize with the backbone chemotherapy administration.

Magrolimab may be withheld if treatment-emergent and/or related AEs occur, and will require consultation with the sponsor if the delay is longer than 3 days. 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 every-3-weeks schedule.

The repriming guidelines shown in Table 4 should be followed for patients with magrolimab dose delays. During repriming, cycle numbering and efficacy, biomarker, PK, and immunogenicity assessments should continue as per assigned cycle number. The safety assessment should follow the Cycle 1 safety assessments and switch back to assigned cycle schedule subsequently. If repriming is necessary before the patient completes Cycle 1 or Cycle 2, the repriming cycle is administered by repeating Cycle 1 dosing, followed by Cycle 2 before proceeding to usual scheduling.

Criteria for permanent discontinuation of magrolimab include the following:

- Grade 4 IRR, as described in Section 7.8.1
- 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. Magrolimab may be withheld if treatment-emergent and/or magrolimab-related AEs occur, until clinical resolution or improvement per the treating physician.

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 4. Repriming Guidelines for Magrolimab

Dose	Dosing frequency	Minimum duration of treatment gap 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
	Every 3 weeks	4 weeks
30 mg/kg	Weekly (during Cycles 1 and/or 2)	4 weeks
	Every 3 weeks	4 weeks
45 mg/kg	Every 3 weeks	4 weeks
60 mg/kg	Every 3 weeks	4 weeks

NA = not applicable

If planned surgical procedures are needed for patients on study treatment, magrolimab will be delayed and restarted in accordance with Table 5.

Table 5. 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

5.6. 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 during subsequent infusions may be continued based on the treating physician's clinical judgment and the presence/severity of prior IRRs. Guidance is provided in Section 7.8.1.2.

Premedications 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. If less than 4 hours has elapsed since a prior dose of acetaminophen has been given, the dose of acetaminophen premedication may be omitted.

5.7. Prior and Concomitant Medications

5.7.1. Prior and Concomitant Medications With Magrolimab

5.7.1.1. Permitted Concomitant Medications

Premedication and prophylaxis for AEs is permitted while on study treatment. Palliative, localized non-CNS radiotherapy to areas of nontarget disease, erythroid and/or myeloid growth factors, hormonal therapy, LHRH agonists for prostate cancer, hormonal maintenance therapy for breast cancers, and treatment with bisphosphonates/RANKL inhibitors are permitted. 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 transfusion are permitted during the study as clinically indicated and 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 are to be recorded in the eCRF. Only the drug name, indication, route, and dates of concomitant medications will be captured in the eCRF.

There are no substantial safety data regarding the concomitant administration of the COVID-19 vaccines and magrolimab. Patients are allowed to receive the COVID-19 vaccine, and study visits should continue as planned if vaccination occurs while the patient is on the study. Investigators should follow local guidelines for concomitant administration of the COVID-19 vaccines with the study drugs.

5.7.1.2. Prohibited Concomitant Medications

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

5.7.2. Prior and Concomitant Medications With Docetaxel

The current prescribing information should be followed for permitted and prohibited concomitant medications.

5.8. Dosage and Administration of Docetaxel

The docetaxel dosing regimens for Safety Run-in Cohort 1 and Phase 2 Cohort 1 are described in Table 2 and Table 3, respectively.

5.9. Docetaxel Premedication and Prophylaxis

For docetaxel treatment, all patients should be premedicated to reduce the incidence and severity of hypersensitivity reactions and fluid retention per their institutional standard of care or as follows. Such premedication may consist of oral corticosteroids such as dexamethasone 16 mg per day (eg, 8 mg twice daily) for 3 days starting 1 day prior to docetaxel. For instances when a patient does not start oral corticosteroids prior to docetaxel administration, IV dexamethasone per institutional standard of care can be given prior to docetaxel administration.

5.10. Dose Modifications for Docetaxel

Docetaxel is known to cause neutropenia, hepatotoxicity, peripheral neuropathy, fluid retention, and hypersensitivity reactions. Dose reductions per key toxicities are described below as recommendations and are in accordance with the docetaxel prescribing information. Additional toxicity management guidelines are provided in docetaxel prescribing information.

5.10.1. Neutropenia

Docetaxel causes neutropenia; guidance on dose reductions are shown in Table 6. Patients should have an ANC of at least 1500 cells/μL before initiating the next cycle of docetaxel therapy. Myeloid growth factor support is allowed per institutional guidelines.

Table 6. Docetaxel Dose Modifications for Neutropenia

Hematologic Toxicity	Occurrence	Docetaxel Dose per Cycle (mg/m^2)[a]
Neutropenic fever (nadir ANC < 500 cells/µL with fever > 38 °C) for > 7 days despite growth factor support Delay of next cycle by > 14 days for nadir ANC < 1500 cells/µL or Nadir ANC < 500 cells/µl for > 7 days	First	55
	Second	37.5
	Third	Discontinue treatment

ANC = absolute neutrophil count

a If docetaxel is dose de-escalated in Safety Run-in Cohort 1 and this dose is utilized in Phase 2, then dose reductions should follow the next lowest dose. For example, if a 55 mg/m^2 docetaxel dose is selected with magrolimab (as part of dose de-escalation), then in the first instance of toxicity, docetaxel should be dose reduced to 37.5 mg/m^2. If a 37.5 mg/m^2 docetaxel dose is selected with magrolimab (as part of dose de-escalation), then in the first instance of toxicity, docetaxel would be discontinued.

5.10.2. Hepatic Toxicity

Docetaxel should be withheld for Grade 3 or 4 hepatic toxicity deemed related to docetaxel as specified in Table 7. Given that magrolimab can cause transient increase in indirect bilirubin due to on-target anemia, dose modifications for docetaxel 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 docetaxel.

Table 7. Docetaxel Dose Reductions for Hepatic Toxicity

Hepatic Toxicity	Occurrence	Docetaxel Dose Modification[a]
AST or ALT level > 1.5 × ULN (or baseline if higher) and alkaline phosphatase > 2.5 × ULN **or** Bilirubin level > 1.25 × ULN (not attributed to magrolimab and is mostly direct)	First	Interrupt treatment until AST/ALT level is ≤ 1.5 × ULN **and** alkaline phosphatase level is ≤ 2.5 × ULN, then reduce to 55 mg/m^2. Interrupt treatment until bilirubin ≤ 1.25 × ULN, then reduce to 55 mg/m^2. If toxicity does not resolve to above criteria within 3 weeks, discontinue treatment.
	Second	Interrupt treatment until AST/ALT level is < 1.5 × ULN **and** alkaline phosphatase level is ≤ 2.5 × ULN, then reduce to 37.5 mg/m^2. Interrupt treatment until bilirubin ≤ 1.25 × ULN, then reduce to 37.5 mg/m^2. If toxicity does not resolve to above criteria within 3 weeks, discontinue treatment.
	Third	Discontinue treatment
AST or ALT > 3 × ULN (or baseline if higher) **and** bilirubin > 2 × ULN (not attributed to magrolimab and is mostly direct)	Any	Discontinue treatment
Bilirubin > 5 × ULN (not attributed to magrolimab and is mostly direct)	Any	Discontinue treatment
AST or ALT > 5 to 10 × ULN for > 2 weeks **or** AST or ALT > 10 × ULN or baseline	Any	Discontinue treatment

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

a If docetaxel is dose de-escalated in Safety Run-in Cohort 1 and this dose is utilized in Phase 2, then dose reductions should follow the next lowest dose. For example, if a 55 mg/m^2 docetaxel dose is selected with magrolimab (as part of dose de-escalation), then in the first instance of toxicity, docetaxel should be dose reduced to 37.5 mg/m^2. If a 37.5 mg/m^2 docetaxel dose is selected with magrolimab (as part of dose de-escalation), then in the first instance of toxicity, docetaxel would be discontinued.

5.10.3. Peripheral Neuropathy

Patients who develop ≥ Grade 3 peripheral neuropathy related to docetaxel should have docetaxel discontinued permanently.

5.10.4. Other Toxicities

Table 8 shows the docetaxel dose modifications for other Grade 3 or 4 hematologic or nonhematologic toxicities deemed related to docetaxel. Docetaxel should be delayed until improvement of Grade 3 or 4 toxicity to at least Grade 2 or better or baseline.

Table 8. Docetaxel Dose Modifications for Other Grade 3/4 Toxicities

Other Toxicity	Occurrence	Docetaxel Dose per Cycle (mg/m^2)[a]
Grade 3 or 4 nonhematologic or hematologic toxicity[b] that does not resolve to ≤ Grade 2 within 14 days	First	55
	Second	37.5
	Third	Discontinue treatment

a If docetaxel is dose de-escalated in Safety Run-in Cohort 1 and this dose is utilized in Phase 2, then dose reductions should follow the next lowest dose. For example, if a 55 mg/m^2 docetaxel dose is selected with magrolimab (as part of dose de-escalation), then in the first instance of toxicity, docetaxel should be dose reduced to 37.5 mg/m^2. If a 37.5 mg/m^2 docetaxel dose is selected with magrolimab (as part of dose de-escalation), then in the first instance of toxicity, docetaxel would be discontinued.
b Grade 3 or 4 nonhematologic or hematologic toxicities apply to those not described in the above dose modification sections.

5.11. 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

5.11.1. 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 study 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 and Appendix Table 2, 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.

All patients will receive magrolimab + docetaxel.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Patients will be screened within 30 days before dosing on Cycle 1 Day 1 to determine eligibility for participation in the study. Data from assessments performed as part of standard of care prior to obtaining informed consent signature may be used if they are within the required screening period. The following will be performed and documented at screening per Appendix 3:

- Obtain written informed consent
- Obtain medical history including concomitant medications
- Obtain demographic information
- Complete physical examination, including vital signs, body weight, and height
- Obtain blood and urine samples for the following tests: chemistry, hematology, coagulation, urinalysis, serum pregnancy, extended RBC phenotyping or genotyping, type, and screen, and direct antiglobulin test. Blood for biomarker samples will also be collected (ie, PBMC [at selected sites], serum and plasma, and whole blood RNA).
- Tumor biopsy
- ECOG
- Perform 12-lead electrocardiogram (ECG; single)
- Record all serious AEs (SAEs) and AEs related to protocol-mandated procedures occurring after signing of the informed consent form (ICF)

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

6.3. Randomization

Randomization will not be performed in this study.

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 $\geq$ 54 years of age with cessation of previously occurring menses for $\geq$ 12 months without an alternative cause. In addition, women of < 54 years of age with amenorrhea of $\geq$ 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 per the duration of required contraception as discussed in Appendix 6. Testing during survival follow-up may be done at home and the result self-reported by the patient. For further details, refer to Appendix 6.

6.4.2. Type and Screen and Direct Antiglobulin Test

Please refer to Section 7.8.1.1 for detailed guidance on type and screen and direct antiglobulin test.

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 and docetaxel at the visits specified in the schedules of assessments in Appendix 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 7).

6.4.6. Electrocardiograms

A single ECG will be performed at screening.

6.4.7. 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.

6.4.8. 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 3).

6.5. Safety Assessments

Table 9 presents analytes to be assessed by the local and/or central laboratory or specialty laboratories at screening. Refer to Section 7.8.1.1 for hemoglobin testing requirements for the first 2 magrolimab doses predose and postdose monitoring.

Table 9. Screening Laboratory Analytes

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

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; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell

Note: Analytes are required to be collected at screening. Refer to Appendix Table 1 for collection time points.

a Reflex microscopic testing based on other abnormalities.

Table 10 presents analytes to be assessed by the local and/or central laboratory or specialty laboratories during the study.

Table 10. Study Laboratory Analytes

Chemistry (Serum or Plasma)	Hematology	Other Laboratory Measurements
Sodium	RBC	Pregnancy (urine or serum)
Potassium	Hemoglobin	Blood samples correlative studies [a]
Chloride	Hematocrit	Pharmacokinetics
Bicarbonate	Platelets	Antidrug antibodies [a]
Total protein	WBC total	
Albumin	WBC differential	
Calcium	Absolute and percent neutrophil count	
Magnesium	Absolute and percent eosinophils	
Phosphorus	Absolute and percent basophils	
Glucose	Absolute and percent lymphocytes	
BUN or urea	Absolute and percent monocytes	
Creatinine	Reticulocytes	
Uric acid		
Total bilirubin		
Direct bilirubin		
Indirect bilirubin		
AST (SGOT)		
ALT (SGPT)		
Alkaline phosphatase		
Haptoglobin		
LDH		

ABO = any of the 4 blood groups A, B, AB, and O comprising the ABO system; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; LDH = lactate dehydrogenase; RBC = red blood cell; Rh = rhesus; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell
Note: Analytes are required to be collected at visits during study. Refer to Appendix Table 1 for collection time points.
a These assays will be performed at a central laboratory.

6.6. Efficacy Assessments

Either contrast-enhanced computed tomography (CT), gadolinium-enhanced magnetic resonance imaging, or positron emission tomography-CT (that includes a contrast-enhanced CT component) of the chest, abdomen, and pelvis will be performed at screening, every 9 weeks (21-day dosing cycle) during the study (starting from Cycle 1 Day 1) and at the end-of-treatment (EOT) visit if one has not been performed within the last 30 days or progressive disease has been documented. The on-treatment imaging window is ± 7 days. Tumor burden will be evaluated solely based on radiographic imaging per RECIST, Version 1.1. Chest x-ray, ultrasound, endoscopy, laparoscopy, positron-emission tomography, radionuclide scans, or tumor markers will not be considered for response assessment.

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.

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. During the treatment phase, scans may be performed at time points other than every 9 weeks (21-day dosing cycle) as clinically indicated to assess tumor progression.

For patients who stop study treatment not related to radiographic disease progression (eg, experienced unexpected toxicity), scans should continue to be collected approximately every 9 weeks (21-day dosing cycle) until radiographic disease progression (ie, preprogression visit [Appendix Table 2]) or initiation of systemic antitumor therapy other than the study treatment, whichever is earlier. Pre-progression visits will be completed first before proceeding to survival follow-up.

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 {Eisenhauer 2009} for the primary efficacy endpoint and for the secondary efficacy endpoint (Appendix 8).

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 according to the schedules of assessments in Appendix Table 3 (note the additional sample collected postdose on Cycle 3 Day 1 at 1 h ± 15 min after the end of magrolimab infusion). Residual samples used for PK and ADA analysis may also be used for CCI PK or PD analyses related to magrolimab treatment alone as well as combination therapy with anticancer chemotherapies. This could include using leftover serum for CCI alternative PK assay development and analysis.

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 3). 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 schedule is outlined in Appendix Table 3.

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.

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 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 2. 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 after safety follow-up [± 7 days]). 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 a serious adverse event (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 end of treatment per the duration of required contraception as discussed in Appendix 6. 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). In 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 2), 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 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. Poststudy treatment assessments are described in Appendix Table 2.

6.14. Sample Storage

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

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, Authorized AxMPs, and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug and AxMP 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).

When there is a reasonable possibility that the causality of the AE/SAE can be assigned to the authorized AxMP, the investigator or qualified subinvestigator will need to report the causality assessment for the authorized AxMPs in accordance with the eCRF.

7.2.2. Assessment of Severity

The severity of AEs will be graded using the NCI CTCAE, Version 5.0. For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale (Appendix 5).

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

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

7.3.2. Adverse Events

Following initiation of study medication, 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 will 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 patient first consents to participate in the study (ie, signing the ICF) 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 with 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: PPD

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

PPD

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: PPD

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

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

7.4.2.3. Pregnancy Reporting Process

The investigator will report pregnancies in female study 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 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 PPD

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

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

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

The patient will 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: PPD

Refer to Appendix 6 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 ($\geq 3 \times$ ULN), AND
- Treatment-emergent total bilirubin elevation ($> 2 \times$ ULN), and absence of cholestasis (defined as alkaline phosphatase $< 2 \times$ 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, extended RBC phenotyping or genotyping, and direct antiglobulin test (DAT) need to be performed at screening before exposure to magrolimab, as described in Section 7.8.1.1.1.

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.

7.8.1.1.1. 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's 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 hemoglobin of about 0.5 g/dL to 1.5 g/dL observed in the first 1 to 2 weeks of treatment. This decrease in hemoglobin level has 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 in hemoglobin level (2 g/dL or higher) have also been observed in early doses.

Patients with a low baseline hemoglobin 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.

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. Hemoglobin should be monitored frequently for response and/or toxicity prior to each dose and 3 to 6 hours after the initiation of the first and second doses of magrolimab. Blood transfusions should be considered as clinically appropriate. Consider additional hemoglobin monitoring during the first week of magrolimab treatment in patients with symptoms of anemia or at increased risk for complications of anemia.

Prior to initiation of magrolimab, ABO/Rh type and screen, DAT, and extended RBC phenotyping (including minor antigens such as Rh, CcEe, Cw, MNSs, Kk, Fya, Fyb, Jka, and Jkb) are to be performed for each patient. Red blood cell genotyping instead of extended RBC phenotyping is acceptable for any patient. Red blood cell genotyping (instead of an extended 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.

7.8.1.1.2. 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.

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. However, CMV-seronegative units for CMV-seronegative patients will not be required for this study.

In case ABO/Rh type cannot be resolved, use pretreatment phenotype/genotype-matched units for minor RBC antigens (CcEe and Kk, to the feasible extent). Regarding the ABO type, the institution can use 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 alloadsorptions with papain-treated RBC samples, pooled single donor apheresis platelets, or commercial human platelet concentrate product if required {Troughton 2018, Velliquette 2019}.

7.8.1.2. 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 5). 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 5.6 will be used to manage IRRs preemptively.

Recommendations for the management of IRRs related to magrolimab are provided in Table 11.

Table 11. Management of Infusion-related Reactions

Infusion-Related Reactions	
CTCAE Grade	**Management**
Grade 1 Mild transient reaction.	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.
Grade 2 Requiring symptomatic treatment and prophylactic medications for ≤ 24 hours.	Interrupt magrolimab therapy per protocol and 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 IRRs 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.

Infusion-Related Reactions	
CTCAE Grade	**Management**
	Patients who experience a Grade 2 infusion-related reaction during the postinfusion observation period that does not resolve to ≤ Grade 1 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.
Grade 3-4 Grade 3: Prolonged reactions or recurrence of symptoms following initial improvement, or where hospitalization is indicated for other clinical sequelae. Grade 4: 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 SC 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 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.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic case report form; IRR = infusion-related reaction; IV = intravenous; SC = subcutaneous

7.8.1.3. 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 12 and follows American Society of Clinical Oncology (ASCO) guidelines for immune-related AEs {Brahmer 2018}. Patients who experience Grade 3 or 4 pneumonitis will be permanently discontinued from study treatment.

Table 12. 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 re-imaging 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

7.8.1.4. 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.

7.8.1.5. Severe Neutropenia

Severe neutropenia and febrile neutropenia have been reported in patients treated with magrolimab. Close monitoring of hematologic parameters (Appendix Table 1 and Appendix Table 2) including neutrophils is required for all patients treated with magrolimab.

Prophylactic antibiotics and/or antimycotics should be considered. Administer granulocyte-colony stimulating factor if clinically indicated.

Recommendations for magrolimab dose delay in case of severe neutropenia:

- For Grade 3 neutropenia 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 or higher 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 neutropenia or febrile neutropenia (> 2 occurrences), discontinuation of magrolimab can be considered.

7.8.1.6. 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 serious infections, hold magrolimab until the infection has resolved clinically. For serious infections that remain active for ≥ 14 days, consider discontinuation of magrolimab.

7.8.2. Docetaxel

Safety management guidelines for docetaxel are described in Section 5.3.3. Additional safety guidelines are provided in the docetaxel prescribing information. Docetaxel prescribing information provides guidance on administration, contraindications, special warnings and precautions, as well as interaction with other medicinal products.

8. STATISTICAL CONSIDERATIONS

This section provides a high-level description of the planned analyses and assessed sample sizes with assumptions. Additional details of the statistical methods will be provided in the statistical analysis plan, including any deviations from the original statistical analyses planned.

8.1. Analysis Objectives and Endpoints

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 Safety Run-in Cohort 1, 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 required dosing cycles (21 days) and the follow-up period as defined in Section 3.1.1. Safety assessments (eg, AEs, ECG, laboratory results) will be displayed by cohort to facilitate dose de-escalation decisions.

8.2.2. Primary Analysis

For each of the subcohorts in Phase 2 Cohort 1, the primary analysis of ORR will be conducted at least approximately 6 months after the last patient is enrolled, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized for the analysis.

8.2.3. Final Analysis

A 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. Modified ITT Analysis Set

The modified ITT Analysis Set includes all enrolled patients who took at least 1 dose of any study drug. This is the primary analysis set for efficacy analyses of Phase 2 Cohorts 1a, 1b, and 1c.

8.3.1.2. Safety Analysis Set

The Safety Analysis Set includes all patients who took at least 1 dose of any study drug. This is the primary analysis set for safety analyses (except for DLTs) of both Safety Run-in Cohort 1 and Phase 2 Cohorts 1a, 1b, and 1c.

8.3.1.3. Dose-Limiting Toxicity Evaluable Analysis Set

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

- 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 1 dose of docetaxel in Safety Run-in Cohort 1.

8.3.1.4. 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.

8.3.1.5. 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.

8.3.1.6. 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 group 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 nonnormality, 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, and ECOG performance status.

8.5. Efficacy Analysis

8.5.1. Primary Efficacy Endpoint Analysis

For Phase 2 Cohort 1, ORR along with the 95% CI based on the Clopper-Pearson method will be estimated for each cohort (Phase 2 Cohorts 1a, 1b, and 1c). 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

For analyses of PFS, OS, and DOR, the KM estimate of the survival function will be computed, and the results will be presented using a KM curve. The median duration will be provided along with corresponding 95% CIs.

8.6. Safety Analysis

8.6.1. Primary Safety Endpoint Analysis

For Safety Run-in Cohort 1, the incidence of DLTs during the DLT assessment period by count and percentage will be reported for Safety Run-in Cohort 1 using the DLT Evaluable Analysis Set. The DLT assessment period is defined as the first cycle (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 will be summarized by cohort (Safety Run-in Cohort 1, Phase 2 Cohorts 1a, 1b, and 1c, respectively). 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

A patient's extent of exposure to study drugs data will be generated from the study drug administration data. Exposure data will be summarized by cohort (Safety Run-in Cohort 1, Phase 2 Cohorts 1a, 1b, and 1c, respectively).

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. A treatment-emergent AE will be defined as any AE that begins on or after the date of the first dose of any study drug up to 30 days after the date of the last dose of any study drug or the day before initiation of subsequent anticancer therapy, whichever occurs first.

Summaries (number and percentage of patients) of treatment-emergent AEs (by system organ class and preferred term) will be provided by cohort (Safety Run-in Cohort 1, Phase 2 Cohorts 1a, 1b, and 1c, respectively).

8.6.5. Laboratory Evaluations

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

Graded laboratory abnormalities will be defined using the grading scheme in Appendix 5.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time point postbaseline, up to and including the date of the last dose of study drug plus 30 days or the day before initiation of new anticancer therapy, whichever is earlier, will be summarized by cohort (Safety Run-in Cohort 1, Phase 2 Cohorts 1a, 1b, and 1c, respectively). 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 will be included in a data listing.

8.6.6. Other Safety Evaluations

Vital signs and physical examination findings will be summarized by cohort (Safety Run-in Cohort 1, Phase 2 Cohorts 1a, 1b, and 1c, respectively). 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

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, as appropriate. CCI

8.10. Sample Size

Table 13 presents the sample size calculations. For Phase 2 Cohort 1, a sample size of 30 patients in the mNSCLC cohort and 40 patients for the mSCLC cohort were calculated using one sample proportion test. The sample size of 26 patients for the mUC cohort was calculated using exact method instead of one sample test due to smaller sample size.

Table 13. Sample Size Calculations

Tumor Type	Sample Size	Null ORR	Alternative ORR	1-sided alpha	Power
mNSCLC	30	13%	25%	0.2	81%
mUC	26	12.4%	28%	0.1	78%
mSCLC	40	9%	20%	0.15	84%

mNSCLC = metastatic non–small cell lung cancer; mSCLC = metastatic small cell lung cancer; mUC = metastatic urothelial cancer; ORR = objective response rate

The null ORR for each of the respective tumor cohorts are based on historical taxane efficacy data in the second line setting {Bellmunt 2017, Rittmeyer 2017, Smit 1998}. Power calculations were performed using EAST 6.5 and nQuery 8.0.

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 GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Gilead, or proprietary interests in the study drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last 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 provide additional samples or to allow the use of the remainder of their already collected specimens for CCI [redacted], 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, 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.

10. REFERENCES

Advani R, Flinn I, Popplewell L, Forero A, Bartlett NL, Ghosh N, et al. CD47 Blockade by Hu5F9-G4 and Rituximab in Non-Hodgkin's Lymphoma. N Engl J Med 2018;379 (18):1711-21.

Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet 2017;389 (10064):67-76.

Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017;376 (11):1015-26.

Brahmer J, Lacchetti C, Schneider B, Atkins M, Brassil K, Caterino J, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. Journal of clinical Oncology 2018;36 (17).

Chao MP, Alizadeh AA, Tang C, Jan M, Weissman-Tsukamoto R, Zhao F, et al. Therapeutic antibody targeting of CD47 eliminates human acute lymphoblastic leukemia. Cancer Res 2011a;71 (4):1374-84.

Chao MP, Alizadeh AA, Tang C, Myklebust JH, Varghese B, Gill S, et al. Anti-CD47 antibody synergizes with rituximab to promote phagocytosis and eradicate non-Hodgkin lymphoma. Cell 2010a;142:699-713.

Chao MP, Jaiswal S, Weissman-Tsukamoto R, Alizadeh AA, Gentles AJ, Volkmer J, et al. Calreticulin Is the Dominant Pro-Phagocytic Signal on Multiple Human Cancers and Is Counterbalanced by CD47. Science translational medicine 2010b;2 (63):63ra94.

Chao MP, Majeti R, Weissman IL. Programmed cell removal: a new obstacle in the road to developing cancer. Nat Rev Cancer. 2012;12 (1):58-67.

Chao MP, Tang C, Pachynski RK, Chin R, Majeti R, Weissman IL. Extranodal dissemination of non-Hodgkin lymphoma requires CD47 and is inhibited by anti-CD47 antibody therapy. Blood 2011b;118 (18):4890-901.

Chen JY, McKenna KM, Choi TS, Duan J, Brown L, Stewart JJ, et al. RBC-Specific CD47 Pruning Confers Protection and Underlies the Transient Anemia in Patients Treated with Anti-CD47 Antibody 5F9 [Abstract]. Blood (ASH Annual Meeting Abstracts) 2018;132 (Suppl 1):2327.

Edris B, Weiskopf K, Volkmer AK, Volkmer JP, Willingham SB, Contreras-Trujillo H, et al. Antibody therapy targeting the CD47 protein is effective in a model of aggressive metastatic leiomyosarcoma. Proc Natl Acad Sci U S A 2012;109 (17):6656-61.

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 (2):228-47.

Ettinger DS, Wood DE, Aggarwal C, Aisner DL, Akerley W, Bauman JR, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 1.2020. J Natl Compr Canc Netw 2019;17 (12):1464-72.

Fisher GA, Lakhani NJ, Eng C, Hecht JR, Bendell JC, Philip PA, et al. A phase Ib/II study of the anti-CD47 antibody magrolimab with cetuximab in solid tumor and colorectal cancer patients [Abstract 114]. Gastrointestinal Cancers Symposium; 2020 23-25 January; San Francisco, CA.

Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med 2018;379 (23):2220-9.

Jaiswal S, Jamieson CH, Pang WW, Park CY, Chao MP, Majeti R, et al. CD47 Is Up-Regulated on Circulating Hematopoietic Stem Cells and Leukemia Cells to Avoid Phagocytosis. Cell 2009;138 (2):271-85.

Kim D, Wang J, Willingham SB, Martin R, Wernig G, Weissman IL. Anti-CD47 antibodies promote phagocytosis and inhibit the growth of human myeloma cells. Leukemia 2012;26 (12):2538-45.

Liu J, Wang L, Zhao F, Tseng S, Narayanan C, Shura L, et al. Pre-Clinical Development of a Humanized Anti-CD47 Antibody with Anti-Cancer Therapeutic Potential. PLoS One. 2015a;10 (9):e0137345.

Liu X, Pu Y, Cron K, Deng L, Kline J, Frazier WA, et al. CD47 blockade triggers T cell-mediated destruction of immunogenic tumors. Nat Med 2015b;21 (10):1209-15.

Majeti R, Chao MP, Alizadeh AA, Pang WW, Jaiswal S, Gibbs KD, Jr., et al. CD47 Is an Adverse Prognostic Factor and Therapeutic Antibody Target on Human Acute Myeloid Leukemia Stem Cells. Cell 2009;138 (2):286-99.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5 (6):649-55.

Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019;394 (10212):1929-39.

Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389 (10066):255-65.

Rossi A, Di Maio M, Chiodini P, Rudd RM, Okamoto H, Skarlos DV, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. J Clin Oncol 2012;30 (14):1692-8.

Sallman DA, Asch A, Al-Malki M, Lee D, Garcia-Manero G, Donnellan W, et al. Tolerability and Efficacy of the First-in-Class Anti-CD47 Antibody Magrolimab Combined With Azacitidine in MDS and AML Patients: Phase 1b Results [Presentation]. American Society of Clinical Oncology (ASCO) Annual Meeting Virtual; 2020.

Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18 (10):2095-103.

Sikic BI, Lakhani N, Patnaik A, Shah SA, Chandana SR, Rasco D, et al. First-in-Human, First-in-Class Phase I Trial of the Anti-CD47 Antibody Hu5F9-G4 in Patients With Advanced Cancers. J Clin Oncol 2019;37 (12):946-53.

Sikic BI, Padda SK, Shah SA, Colevas AD, Narayanan S, Fisher GA, et al. A first-in-human, first-in-class phase I trial of the anti-CD47 antibody Hu5F9-G4 in patients with advanced cancers. 2016:

Smit EF, Fokkema E, Biesma B, Groen HJ, Snoek W, Postmus PE. A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. Br J Cancer 1998;77 (2):347-51.

Taxotere®, Gilead Sciences Inc. Taxotere® (docetaxel) Summary of Product Characteristics. Foster City, CA. Revised 06/2020. 1995:

Taxotere®, Gilead Sciences Inc. Taxotere® (docetaxel) Injection Concentrate, Intravenous Infusion. U.S. Prescribing Information. Foster City, CA. Revised 05/2021. 1996:

Troughton MC, Simmons LW, Langley C, Youssef M, Marques MB. A Novel Use of Human Platelet Concentrate to Resolve Interference of Anti-CD47 in Serologic Testing [IGT46]. Transfusion 2018;58 (S2):179A-80A.

Tseng D, Volkmer JP, Willingham SB, Contreras-Trujillo H, Fathman JW, Fernhoff NB, et al. Anti-CD47 antibody-mediated phagocytosis of cancer by macrophages primes an effective antitumor T-cell response. Proc Natl Acad Sci U S A 2013;110 (27):11103-8.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July, 2009.

Van Cutsem E, Mayer RJ, Laurent S, Winkler R, Gravalos C, Benavides M, et al. The subgroups of the phase III RECOURSE trial of trifluridine/tipiracil (TAS-102) versus placebo with best supportive care in patients with metastatic colorectal cancer. Eur J Cancer 2018;90:63-72.

Velliquette RW, Aeschlimann J, Kirkegaard J, Shakarian G, Lomas-Francis C, Westhoff CM. Monoclonal anti-CD47 interference in red cell and platelet testing. Transfusion 2019;59 (2):730-7.

von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000;18 (17):3068-77.

Vuky J, Balar AV, Castellano D, O'Donnell PH, Grivas P, Bellmunt J, et al. Long-Term Outcomes in KEYNOTE-052: Phase II Study Investigating First-Line Pembrolizumab in Cisplatin-Ineligible Patients With Locally Advanced or Metastatic Urothelial Cancer. J Clin Oncol 2020;38 (23):2658-66.

Willingham SB, Volkmer JP, Gentles AJ, Sahoo D, Dalerba P, Mitra SS, et al. The CD47-signal regulatory protein alpha (SIRPa) interaction is a therapeutic target for human solid tumors. Proc Natl Acad Sci U S A 2012;109 (17):6662-7.

Yamamoto N, Tsurutani J, Yoshimura N, Asai G, Moriyama A, Nakagawa K, et al. Phase II study of weekly paclitaxel for relapsed and refractory small cell lung cancer. Anticancer Res 2006;26 (1B):777-81.

11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGMENT

A Phase 2, Multi-Arm Study of Magrolimab in Patients with Solid Tumors

GS-US-548-5918 Amendment 5; 24 October 2023

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

PPD

Name (Printed)
Medical Monitor

[See appended electronic signature]

Signature

[See appended electronic signature]

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Marketing Authorization Status of Study Interventions

Study Intervention Name	Category	Authorized in ≥ 1 Country Following EU Regulation No. 536/2014	Authorized in ≥ 1 ICH Country	Authorized by Swissmedic
Magrolimab	Study drug	No[a]	No[a]	No[a]
Docetaxel	Study drug	Yes	Yes	Yes
Acetaminophen	AxMP	Yes	Yes	Yes
Diphenhydramine	AxMP	Yes	Yes	Yes
Dexamethasone	AxMP	Yes	Yes	Yes

AxMP = auxiliary medicinal product; EU = European Union; ICH = International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
a Rationale described in Section 1

Appendix 3. Schedules of Assessment

Appendix Table 1. Safety Run-in Cohort 1 and Phase 2 Cohort 1: 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]	4+[a]
		None		± 3[b]		± 3[b]			± 3[b]	± 3[b]
Cycle Day		1	2	8	15	1	8	15	1	1
Informed consent	X									
Demographics	X									
Medical and cancer history	X									
ECOG	X	X				X			X	X
Vital signs, height, and weight[c]	X	X		X	X	X	X	X	X	X
Physical examination[d]	X	X		X	X	X		X	X	X
ECG (single)	X									
Pregnancy test[e]	X	X				X			X	X
Hematology[b, f]	X	X[f]	X	X[f]	X	X	X	X	X	X
Haptoglobin and LDH[b]		X		X		X				
Serum or plasma chemistry[b]	X	X		X	X	X	X	X	X	X
Coagulation[g]	X									
Blood, type and screen (ABO/Rh), DAT, and extended RBC phenotyping and genotyping	X									
Urinalysis[b, h]	X									
Tumor imaging[i]	X									X, Q9W
Tumor biopsy	Refer to Appendix Table 3									

Visit Window (Days)	Screening Day -30 to -1	Cycle (21-day cycles)								
		1[a]				2[a]			3[a]	4+[a]
		None		± 3[b]		± 3[b]			± 3[b]	± 3[b]
Cycle Day		1	2	8	15	1	8	15	1	1
Adverse events[j]	X	→	→	→	→	→	→	→	→	→
Concomitant medications	X	→	→	→	→	→	→	→	→	→
Receptor occupancy	Refer to Appendix Table 3									
Circulating tumor DNA										
PBMC										
Serum and plasma biomarkers										
Whole blood RNA										
Immunophenotyping assay										
TCR sequencing										
Stool microbiome										
Genomic blood sample										
PK										
Antidrug antibodies										
IRT registration[k]	X	X		X	X	X	X	X	X	X
Premedication for magrolimab[l]		X		X						
Magrolimab[m]		X		X	X	X	X	X	X	X
Docetaxel		X				X			X	X

ABO = any of the 4 blood groups A, B, AB, and O comprising the ABO system; 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; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; Q9W = every 9 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; Rh = rhesus; RP2D = recommended Phase 2 dose; TCR = T cell receptor
Note: Refer to Section 6.5 Safety Assessments for complete list of analytes to be tested.

a In cases of magrolimab repriming following a treatment delay (Section 5.5), efficacy, biomarker, PK, and immunogenicity assessments will follow the schedule of the assigned cycle number. Magrolimab dosing and the safety assessment will follow Cycle 1 (refer to Table 2 or Table 3 as appropriate), and then subsequently switch back to the next assigned cycle schedule. Magrolimab should not be given on consecutive days. Refer to footnote (l) for premedication requirement.

b Pretreatment assessments are to be collected within 3 days prior to any study treatment administration. 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.

c 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.

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

e 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.

f A complete blood count with differential, platelets, and reticulocytes will be conducted. An additional hemoglobin must be checked 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment (refer to Section 7.8.1.1). Pretreatment assessments are to be collected within 24 hours prior to the first 2 magrolimab doses per Section 7.8.1.1.

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

h Reflex microscopic testing based on other abnormalities.

i CT/MRI will be performed per Section 6.6. Per RECIST, Version 1.1, if a patient achieves an initial objective response on imaging, an imaging assessment at least 4 weeks later is required for confirmed response. Confirmation of disease progression through a subsequent response assessment at least 4 weeks apart may also be considered per Section 3.4. The on-treatment imaging window is ± 7 days.

j During screening, collect adverse events related to protocol-mandated procedures.

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

l Premedication with acetaminophen and diphenhydramine is required prior to the administration of the first 2 doses of study treatment and in case of reintroduction with repriming.

m Magrolimab will be administered first before docetaxel. All patients should be monitored hourly during infusion. Patients to be monitored (including measurement of vital signs, as clinically appropriate) for signs and symptoms of IRRs, which have been observed in previous magrolimab studies. Postinfusion monitoring to begin after the infusion is complete but prior to administering docetaxel. Postinfusion monitoring is not required for doses after Cycle 1. The RP2D will be determined in Safety Run-in Cohort 1. The magrolimab dosing regimen is described in Table 2 for Safety Run-in Cohort 1 and Table 3 for Phase 2 Cohort 1.

Appendix Table 2. 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	X
Hematology[d]	X			
Serum or plasma chemistry	X			
Pharmacokinetics	Refer to Appendix Table 3			
Antidrug antibodies				
Receptor occupancy				
Circulating tumor DNA				
Whole blood RNA				
Serum and plasma biomarkers				
Tumor imaging for response assessment[e]	X		X	
ECOG	X			
Vital signs	X			
Symptom-directed physical examination	X			
Adverse events[f]	X	X		
Concomitant medications	X	X		
New anticancer therapy[g]		X	X	X
Survival follow-up				Every 2 months[h]

CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; MRI = magnetic resonance imaging; TCR = T cell receptor

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 not related to radiographic disease progression 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 end of treatment per the duration of required contraception as discussed in Appendix 6. 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 has been documented. CT/MRI will be performed per Section 6.6. For patients who stop study treatment not related to radiographic disease progression (eg, experienced unexpected toxicity), scans should continue to be collected approximately every 9 weeks (21-day dosing cycle) until disease progression or initiation of systemic antitumor therapy other than the study treatment, whichever is earlier.
f Report all AEs through the Safety Follow-up Visit/Call, and any treatment-related SAEs thereafter.
g Collect new anticancer therapy data following the last dose of study treatment until the end of survival follow-up.
h 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 3. Pharmacokinetic, Antidrug Antibodies, and Biomarker: Schedule of Assessments

	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	X		X		X	X		X			X
PBMC[f]		X	X		X	X						
TCR sequencing[f]		X	X		X	X						
Immunophenotyping assay[f]		X	X[g]		X	X						
Serum and plasma biomarkers[h]		X	X[g]		X	X	X		X			X
Whole blood RNA[h]		X	X[g]		X	X	X		X			X
Stool microbiome[i]		X				X						
Genomic blood sample[j]		X										
Tumor biopsy	X					X[k]						

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 end of treatment.

b In Cycle 3, PK samples are to be collected predose (within 12 hours) and post-dose 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 end of treatment.

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 end of treatment, 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 magrolimab on Cycle 1 Day 1 and Cycle 1 Day 15, predose within 12 hours prior to the first administration of magrolimab given in Cycles 3, 4, and 7, and at end of treatment (regardless of time of occurrence).

f Samples will be collected predose within 12 hours prior to administration of magrolimab on Cycle 1 Day 1 and Cycle 1 Day 8, and predose within 12 hours prior to the first administration of magrolimab given in Cycles 2 and 3. PMBC and immunophenotyping will be collected at select sites only.

g For serum and plasma biomarkers, whole blood RNA, and immunophenotyping assay, an additional sample will be collected 4 hours postdose on Cycle 1 Day 8.

h Samples will be collected predose within 12 hours prior to administration of magrolimab on Cycle 1 Day 1 and Cycle 1 Day 8, predose within 12 hours prior to the first administration of magrolimab given in Cycles 2, 3, 4, and 7, and at end of treatment if occurring before Cycle 7.
i Stool microbiome to be collected predose on or before Cycle 1 Day 1 and anytime within 7 days of Cycle 3 Day 1.
j The genomic blood sample can be collected at Cycle 1 Day 1 or at any time during the study.
k On-treatment tumor biopsy can be collected any time between Cycle 3 Day 1 and Cycle 4 Day 1.

Appendix 4. 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. Special pandemic measures can be applied only when in accordance with the current situation and applicable local authority regulations, recommendations, or similar.

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

1) Schedule of assessments:

   a) Physical examination:

      i) 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:

      i) 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 non-investigational product as determined by sponsor (ie, docetaxel) 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:

      i) 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:

   a) 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 trial patients is important and testing of coronavirus disease 2019 (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 the clinical trial 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 of new patients will be placed on hold until the pandemic outbreak is under control by following local regulatory guidelines.

Appendix 5. 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 6. 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 ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of < 54 years of age with amenorrhea of ≥ 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 embryofetal development toxicity study in cynomolgus monkeys and there is a strong suspicion of human fetotoxicity in early pregnancy based on the nonclinical data. For magrolimab, there is no anticipated pharmacokinetic interaction with progestin or other steroids based on the distinct clearance pathways.

Based on the mechanism of action (MOA) and findings in animals, docetaxel can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant during therapy with docetaxel. If the patient becomes pregnant while receiving docetaxel, the patient should be apprised of the potential hazard to the fetus. There is no contraindication to hormonal contraception according to the docetaxel prescribing information.

b. Contraception Requirements for Female 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 < 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 trial 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:
  - — Non-hormonal 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 highly effective 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 not be collected in this study; however, the investigator should reinforce proper contraception use with the study patient if a partner pregnancy is reported. Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.4.2.3.

Appendix 7. 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 8. 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 9. Country-Specific Requirements

Not applicable.

Appendix 10. 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), with changes listed in each table in order of importance. 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 Amendment 4 to this amendment will be made available upon the publication of this protocol.

Amendment 5 (24 October 2023)

Rationale for Key Changes Included in Amendment 5	Affected Sections
Collection period for treatment-emergent adverse events clarified.	Section 8.6.4
Collection period for incidence of treatment-emergent laboratory abnormalities clarified.	Section 8.6.5
Updates made to align with current safety recommendations.	Sections 1.2.3, 1.7, 5.6
Timing of primary analysis for Phase 2 Cohort 1 clarified.	Section 8.2.2
Updated the toxicity management regarding hemoglobin monitoring to align with current recommendations.	Section 7.8.1
Remove circulating tumor cell sample collection as not performed.	Section 3.8; Appendix Tables 1 and 2
Sample size for urothelial cancer cohort updated.	Synopsis; Schema; Sections 3.1, 4.1, and 8.10
Magrolimab administration language updated to clarify vital signs will be assessed prior to administration.	Sections 5.4
Language added to allow local sourcing of docetaxel.	Section 5.3.2
Updated guidance provided for the management of infusion-related reactions.	Section 7.8.1.2 (Table 11)
New sections provided for guidance on management of severe neutropenia and serious infections.	Sections 7.8.1.5 and 7.8.1.6
Text added to align with EU-CTR requirements.	Sections 1.4, 7.2.1, and 9.2.2; Appendices 2 and 9
Text updated to clarify that 'urine or serum pregnancy tests will be conducted from Cycle 1 Day 1' with respect to pregnancy test.	Appendix Table 1 – footnote 'e' and Appendix Table 2
Analysis sets updated.	Section 8.3
Guidance on COVID-19 vaccination provided.	Section 5.7.1.1
Language updated to clarify that a final analysis may be conducted after the primary analysis.	Section 8.2.3
Inclusion criteria were updated for clarification.	Synopsis; Section 4.2
Text was updated to replace 'participants' with 'patients' to maintain consistency.	Appendix 3

Rationale for Key Changes Included in Amendment 5	Affected Sections
Changes from administrative amendment 1 were added to the protocol.	Section 6.2.1
Changes from administrative amendment 2 were added to the protocol.	Synopsis; Section 6.6; Appendix Tables 1 and 2
Minor changes to correct typographic errors.	Throughout, as needed

prot GS-US-548-5918 amd-5

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	25-Oct-2023 15:28:28