CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2 Study of Magrolimab Combination Therapy in Patients With Head and Neck Squamous Cell Carcinoma
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number:	155066
EU CT Number:	2020-005708-20
ClinicalTrials.gov Identifier:	NCT04854499
Indication:	Head and Neck Squamous Cell Carcinoma
Protocol ID:	GS-US-548-5916
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.

Protocol Version/Date:		
	Original:	22 January 2021
	Amendment 1:	12 March 2021
	Amendment 2:	17 March 2021
	Amendment 3:	16 December 2021
	Amendment 4:	26 January 2022
	Amendment 5:	20 September 2022
	Amendment 6:	01 November 2023

This study will be conducted under United States Food and Drug Administration investigational new drug (IND) regulations (21 CFR Part 312); however, sites located in the European Economic Area, United Kingdom, and Switzerland are not included under the IND and are considered non-IND sites.
This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

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PROTOCOL SYNOPSIS

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<tr><td>Study Centers Planned:</td><td>Approximately 100 centers globally</td></tr>
<tr><td>Objectives and Endpoints:</td><td>
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<tr><th>Primary Objectives</th><th>Primary Endpoints</th></tr>
<tr><td>Safety Run-in:
• To evaluate the safety, tolerability, and recommended Phase 2 dose (RP2D) of magrolimab in combination with the following:
— Pembrolizumab + platinum + 5-fluorouracil (5-FU)
— Docetaxel
Phase 2 Cohorts:
• To evaluate the progression-free survival (PFS) with magrolimab in combination with pembrolizumab + platinum + 5-FU versus pembrolizumab + platinum + 5-FU as determined by investigator assessment (Phase 2 Cohort 1)
• To evaluate the efficacy of magrolimab in combination with pembrolizumab, if this optional cohort is opened, and magrolimab in combination with docetaxel as determined by the investigator-assessed objective response rate (ORR) (Phase 2 Cohorts 2 and 3)</td><td>Safety Run-in:
• Incidence of adverse events (AEs) and laboratory abnormalities defined as dose-limiting toxicities (DLTs) according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0
Phase 2 Cohorts:
• PFS, defined as the time from the date of randomization until the earliest date of documented disease progression, as determined by investigator assessment, or death from any cause, whichever occurs first (Phase 2 Cohort 1, Arm A versus Arm B)
• ORR, defined as the proportion of patients who achieve a complete response (CR) or partial response (PR) as measured by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, as determined by investigator assessment (Phase 2 Cohorts 2 and 3)</td></tr>
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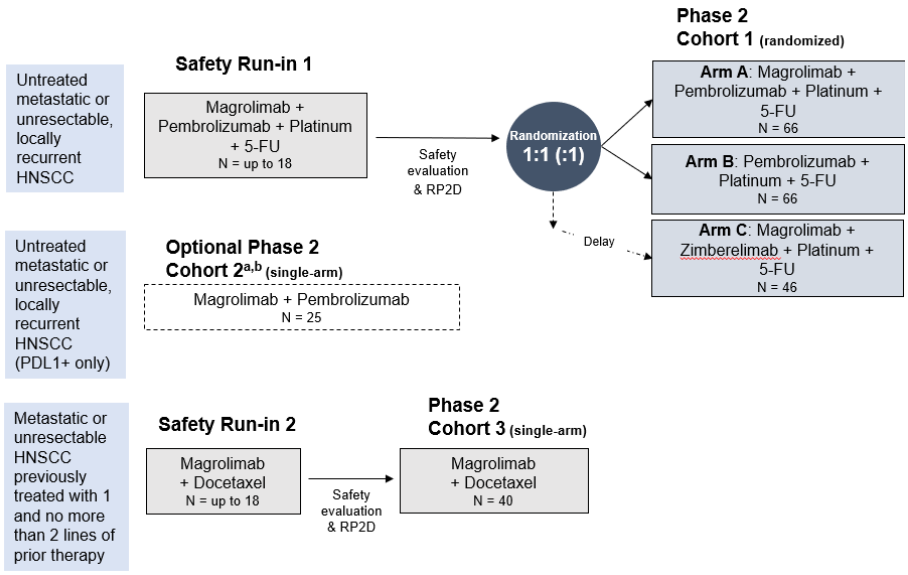
	Secondary Objectives	Secondary Endpoints
	Safety Run-in: • To evaluate the pharmacokinetics (PK) and immunogenicity of magrolimab in combination with anticancer therapies Phase 2 Cohorts: • To evaluate PFS for magrolimab + zimberelimab + platinum + 5-FU versus pembrolizumab + platinum + 5-FU as determined by investigator assessment (Phase 2 Cohort 1) • To evaluate ORR as determined by investigator assessment (Phase 2 Cohort 1) • To evaluate PFS by investigator assessment (Phase 2 Cohorts 2 and 3) • To evaluate additional measures of efficacy, including duration of response (DOR) and overall survival (OS) • To evaluate the PK and immunogenicity of magrolimab in combination with anticancer therapies • To evaluate patient-reported outcomes (PROs)/quality-of-life measures	Safety Run-in: • Magrolimab concentration versus time and antidrug antibodies (ADAs) to magrolimab Phase 2 Cohorts: • PFS as determined by investigator assessment or death from any cause, whichever occurs first (Phase 2 Cohort 1, Arm C versus concurrent Arm B) • ORR as determined by investigator assessment (Phase 2 Cohort 1) • PFS from date of dose initiation (Phase 2 Cohort 2 and Phase 2 Cohort 3) until the earliest date of documented disease progression as determined by investigator assessment per RECIST, Version 1.1, or death from any cause, whichever occurs first • DOR, defined as time from first documentation of CR or PR to the earliest date of documented disease progression or death from any cause, whichever occurs first • OS, defined as time from date of randomization (Phase 2 Cohort 1) or date of dose initiation (Phase 2 Cohort 2 and Phase 2 Cohort 3) to death from any cause • Magrolimab concentration versus time and ADAs to magrolimab • PRO assessment (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core - Questionnaire [EORTC QLQ-C30], European Organisation for Research and Treatment of Cancer Quality of Life - Head and Neck Module [EORTC QLQ-H&N35], and 5 level – EuroQol - 5 dimensions questionnaire [EQ-5D-5L]) scores
	[redacted]	

	CCI
Study Design:	This is a Phase 2, open-label, multicenter study evaluating magrolimab in combination with pembrolizumab + platinum + 5-FU chemotherapy; magrolimab in combination with pembrolizumab; magrolimab in combination with zimberelimab + platinum + 5-FU chemotherapy in patients with untreated metastatic or unresectable, locally recurrent head and neck squamous cell carcinoma (HNSCC); and magrolimab in combination with docetaxel in patients with locally advanced/metastatic HNSCC (mHNSCC) who were previously treated with at least 1 and no more than 2 lines of prior systemic therapy. This study will consist of the following 2 safety run-in evaluations: • **Safety Run-in 1:** magrolimab + pembrolizumab + platinum + 5-FU in patients with untreated metastatic or unresectable, locally recurrent HNSCC regardless of programmed cell death ligand 1 (PD-L1) status • **Safety Run-in 2:** magrolimab + docetaxel in patients with locally advanced/mHNSCC regardless of PD-L1 status who were previously treated with at least 1 and no more than 2 lines of prior systemic therapy Additionally, a pre-expansion safety run-in evaluation of magrolimab + pembrolizumab in patients with untreated metastatic or unresectable, locally recurrent HNSCC with a PD-L1 combined positive score (CPS) ≥ 1 may be conducted at the sponsor's discretion prior to the initiation of the optional Phase 2 cohort of magrolimab + pembrolizumab. Once the Safety Review Team (SRT) reviews the safety for patients in each run-in and the sponsor determines the RP2D for that cohort, the following Phase 2 cohorts will be conducted: • **Phase 2 Cohort 1:** a randomized, open-label cohort of magrolimab + pembrolizumab + platinum + 5-FU (Arm A) versus pembrolizumab + platinum + 5-FU (Arm B) versus a delayed open arm magrolimab + zimberelimab + platinum + 5-FU (Arm C) in patients with untreated metastatic or unresectable, locally recurrent HNSCC regardless of PD-L1 status • **Optional Phase 2 Cohort 2:** a cohort of magrolimab + pembrolizumab in patients with untreated metastatic or unresectable, locally recurrent HNSCC with a PD-L1 CPS ≥ 1

	• **Phase 2 Cohort 3:** a cohort of magrolimab + docetaxel in patients with locally advanced/mHNSCC regardless of PD-L1 status who were previously treated with at least 1 and no more than 2 lines of prior systemic therapy
	The study schematic is provided below.  5-FU = 5-fluorouracil; HNSCC = head and neck squamous cell carcinoma; PD-L1 = programmed cell death ligand 1; RP2D = recommended Phase 2 dose a Optional cohort to be opened at the discretion of the sponsor. b A pre-expansion safety run-in evaluation of magrolimab + pembrolizumab may be conducted at the sponsor's discretion prior to the initiation of this optional cohort. **Safety Run-in 1:** A 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 no more than 2 of 6 DLT-evaluable patients experience a DLT in Cycle 1, enrollment into Phase 2 Cohorts 1 and 2 will begin at this dose level. • If 3 or more (> 34%) DLT-evaluable patients experience a DLT at any time, another 6 patients will be enrolled at a lower dose and will be evaluated in the same manner to define the recommended dose for the combination regimen.

	Pre-expansion Safety Run-in for Magrolimab + Pembrolizumab (if Applicable): At the discretion of the sponsor, 6 patients may be initially enrolled to receive magrolimab + pembrolizumab in this pre-expansion run-in evaluation. Dose evaluation and possible de-escalation will be performed as described for Safety Run-in 1. **Safety Run-in 2:** Safety Run-in 2 will open for enrollment at the same time as Safety Run-in 1. A 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. The same design and DLT rules will apply to Safety Run-in 2. **DLT Assessment Period:** The DLT assessment period will be the first cycle (21 days) and applies to each safety run-in. Patients will be considered evaluable for assessment of DLTs if either of the following criteria is met during the DLT assessment period: • The patient experiences a DLT at any time after initiation of the first infusion of magrolimab. • The patient does not experience a DLT and completes at least 2 infusions of magrolimab and at least 1 dose of pembrolizumab, 1 dose of platinum, and 1 dose of 5-FU for Safety Run-in 1; at least 1 dose of docetaxel for Safety Run-in 2; and at least 1 dose of pembrolizumab for the pre-expansion safety run-in for magrolimab + pembrolizumab (if applicable). 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 evaluations will be replaced. The DLT definition is provided in the study protocol. Patients enrolled in the safety run-in evaluations will continue treatment until unacceptable toxicity or radiographic disease progression, whichever occurs first, and will not change their magrolimab dose level after the RP2D is determined. **Phase 2 Cohort 1 (n = 178):** Once the SRT reviews Safety Run-in 1 and the sponsor determines the RP2D for magrolimab + pembrolizumab + 5-FU + platinum, a Phase 2, randomized, open-label cohort with a 2-treatment-group design will open for enrollment. Approximately 132 patients with untreated metastatic or unresectable, locally recurrent HNSCC regardless of PD-L1 status will be randomized in a 1:1 ratio to receive either magrolimab + pembrolizumab + platinum + 5-FU (Arm A) or pembrolizumab + platinum + 5-FU (Arm B). The primary efficacy assessment will be PFS as determined by investigator assessment, with the primary analysis to occur after 93 events. Stratification factors for randomization include the following: 1) PD-L1 expression (CPS $\geq$ 1 versus CPS < 1) and 2) p16 status (positive versus negative).

	Once the Phase 2 Cohort 1 enrolls 20 patients in each Arm A and Arm B, a third arm will open: magrolimab + zimberelimab + platinum + 5-FU (Arm C; n = 46). Randomization will continue 1:1:1 across all 3 arms, with the stratification factors 1) PD-L1 expression (CPS ≥ 1 versus CPS < 1) and 2) p16 status (positive versus negative). **Phase 2 Cohort 2 (n = 25):** Approximately 25 patients with untreated metastatic or unresectable, locally recurrent HNSCC with a PD-L1 CPS ≥ 1 may be enrolled to receive magrolimab + pembrolizumab in the optional Phase 2 Cohort 2. The primary efficacy assessment will be investigator assessed ORR. **Phase 2 Cohort 3 (n = 40):** Once the SRT reviews Safety Run-in 2 and the sponsor determines the RP2D for magrolimab + docetaxel, Phase 2 Cohort 3 will open for enrollment. Approximately 40 patients with locally advanced/mHNSCC regardless of PD-L1 status who were previously treated with at least 1 and no more than 2 lines of prior systemic therapy will be enrolled to receive magrolimab + docetaxel. The primary efficacy assessment will be investigator-assessed ORR. **Pharmacokinetic and Antidrug Antibody Testing:** Pharmacokinetic (serum) and ADA (peripheral blood) analyses will be performed for patients who receive treatment with magrolimab or zimberelimab. **Diagnostic Tissue Testing:** Tumor expression of PD-L1 will be evaluated prospectively using an assay approved by the Food and Drug Administration for detection of PD-L1 in HNSCC tissues. Testing for p16 human papillomavirus (HPV) positivity will be performed by immunohistochemistry analysis. Oral cavity, hypopharynx, and larynx cancers are not required to undergo HPV testing by immunohistochemistry, as by convention they are assumed to be HPV negative.
Number of Patients Planned:	Approximately 230 patients in total and up to 297: • Safety Run-in 1 and 2: at least 12 and up to 36 patients in total • Optional pre-expansion safety run-in for Cohort 2: possibly 6 patients and up to 18 in total • Phase 2 Cohort 1: approximately 178 patients • Phase 2 Cohort 2 (optional): approximately 25 patients • Phase 2 Cohort 3: approximately 40 patients
Target Population:	**Phase 2 Cohort 1:** Patients previously untreated for metastatic or unresectable, locally recurrent HNSCC regardless of PD-L1 status **Phase 2 Cohort 2:** Patients previously untreated for metastatic or unresectable, locally recurrent HNSCC with a PD-L1 CPS ≥ 1 **Phase 2 Cohort 3:** Patients with locally advanced/mHNSCC regardless of PD-L1 status who were previously treated with at least 1 and no more than 2 lines of prior systemic therapy

Duration of Treatment:	Cycle length is 21 days for all cohorts. All patients will continue on study treatment unless they meet study treatment discontinuation criteria.
Diagnosis and Main Eligibility Criteria:	**Inclusion Criteria:** <u>All Patients</u> 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) Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1. 5) Laboratory measurements, blood counts: a) Hemoglobin must be ≥ 9 g/dL prior to initial dose of study treatment. Red blood cell transfusions are allowed to meet hemoglobin eligibility within limits set per Exclusion Criterion #6. b) Absolute neutrophil count ≥ 1.5×10^9/L c) Platelets ≥ 100×10^9/L 6) Laboratory measurements, renal function: a) Serum creatinine ≤ 1.5 × upper limit of normal (ULN) or if elevated, a calculated glomerular filtration rate > 40 mL/min/1.73 m^2 7) Laboratory measurements, hepatic function: a) Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 × ULN or ≤ 5 × ULN in patients with liver metastases b) Total bilirubin ≤ 1.5 × ULN or ≤ 3.0 × ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or genetic equivalent 8) Laboratory measurements, coagulation function: a) International normalized ratio or prothrombin time (PT) ≤ 1.5 × ULN unless patient is receiving anticoagulation therapy, as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use for anticoagulants b) Activated partial thromboplastin time or PTT ≤ 1.5 × ULN unless patient is receiving anticoagulation therapy, as long as PT or PTT is within therapeutic range of intended use for anticoagulants 9) Pretreatment blood cross-match completed.

	10) Male and female patients of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception. 11) Measurable disease according to RECIST, Version 1.1. 12) Note: Inclusion Criterion #12 was removed in Protocol Amendment 3 and relocated to Inclusion Criterion #13d. <u>Safety Run-in 1, Pre-expansion Safety Run-in for Magrolimab + Pembrolizumab (if Applicable), and Phase 2 Cohorts 1 and 2</u> In addition to meeting the inclusion criteria for all patients, patients who are enrolled into Safety Run-in 1, the pre-expansion safety run-in for magrolimab + pembrolizumab (if applicable), and Phase 2 Cohorts 1 and 2 must fulfill the following cohort-specific inclusion criterion: 13) Patients with histologically or cytologically confirmed metastatic or locally recurrent HNSCC that is considered incurable by local therapies a) Patients should not have had prior systemic therapy administered in the recurrent or metastatic setting. Systemic therapy that was completed more than 6 months prior to signing consent if given as part of multimodal treatment for locally advanced disease is allowed. b) Eligible primary tumor locations include oropharynx, oral cavity, hypopharynx, and larynx. c) Patients may not have a primary tumor site of nasopharynx (any histology). d) Patients must be willing to provide baseline tumor tissue from a core or excisional biopsy (fine needle aspirate is not adequate). A newly obtained biopsy (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 be requested to consent to a mandatory on-treatment tumor biopsy, unless not feasible as determined by the investigator and discussed with the sponsor. <u>Safety Run-in 1 and Phase 2 Cohort 1</u> In addition to meeting the inclusion criteria for all patients, patients who are enrolled into Safety Run-in 1 and Phase 2 Cohort 1 must fulfill the following cohort-specific inclusion criterion: 14) Patients with HNSCC per Inclusion Criterion #13 regardless of PD-L1 status

	Pre-expansion Safety Run-in for Magrolimab + Pembrolizumab (if Applicable) and Phase 2 Cohort 2 In addition to meeting the inclusion criteria for all patients, patients who are enrolled into the pre-expansion safety run-in for magrolimab + pembrolizumab (if applicable) and Phase 2 Cohort 2 must fulfill the following cohort-specific inclusion criterion: 15) Patients with HNSCC per Inclusion Criterion #13 with a PD-L1 CPS ≥ 1 Safety Run-in 2 and Phase 2 Cohort 3 In addition to meeting the inclusion criteria for all patients, patients who are enrolled into Safety Run-in 2 and Phase 2 Cohort 3 must fulfill the following cohort-specific inclusion criterion: 16) Patients with histologically or cytologically confirmed locally advanced/mHNSCC regardless of PD-L1 status with at least 1 and no more than 2 lines of prior systemic anticancer therapy in the locally advanced/metastatic setting a) Eligible primary tumor locations include oropharynx, oral cavity, hypopharynx, and larynx. b) Patients may not have a primary tumor site of nasopharynx (any histology). c) Prior systemic anticancer therapy for locally advanced/mHNSCC should consist of at least 1 line of platinum-based chemotherapy, with or without a PD-1 inhibitor. For patients with CPS ≥ 1 HNSCC, prior systemic anticancer therapy for locally advanced/mHNSCC should have included at least one line of PD-1 inhibitor-based therapy unless medically contraindicated. **Exclusion Criteria:** All Patients 1) Prior radiation therapy (or other nonsystemic therapy) within 2 weeks prior to enrollment. Patients who are candidates for curative radiation therapy are not eligible. 2) Patient has not fully recovered (ie, ≤ Grade 1 at baseline) from AEs due to a previously administered treatment. a) Note: Patients with ≤ Grade 2 neuropathy, ≤ Grade 2 alopecia, or laboratory values in inclusion criteria 5 through 8 are exceptions to this criterion and may qualify for the study. b) Note: If a patient received major surgery, he or she must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

	3) Positive serum pregnancy test (Appendix 5). 4) Breastfeeding female. 5) Active central nervous system (CNS) disease (patients with asymptomatic and stable, treated CNS lesions who have been off corticosteroids, radiation, or other CNS-directed therapy for at least 4 weeks are not considered active). 6) Red blood cell transfusion dependence, defined as requiring more than 2 units of packed red blood cell 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 criterion. 7) History of hemolytic anemia, autoimmune thrombocytopenia, or Evans syndrome in the last 3 months. 8) Known hypersensitivity to any of the study drugs, the metabolites, or formulation excipient. a) For Phase 2 Cohort 1, complete absence of dihydropyrimidine dehydrogenase (DPD) activity. If DPD status is not known, testing for DPD status should be done during the screening period where such testing is standard of care. 9) Prior treatment with cluster of differentiation 47 or signal regulatory protein alpha-targeting agents. 10) Prior anticancer therapy including, but not limited to, chemotherapy, immunotherapy, or investigational agents within 4 weeks prior to magrolimab treatment. 11) Life expectancy of less than 3 months and/or rapidly progressing disease (eg, tumor bleeding, uncontrolled tumor pain) in the opinion of the treating investigator. 12) Diagnosis of immunodeficiency or receipt of systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study therapy. Corticosteroid use as a premedication for allergic reactions or for prophylactic management of AEs related to the chemotherapies specified in the protocol is allowed. The use of physiologic doses of corticosteroids may be approved with approval by the sponsor. 13) Active autoimmune disease that has required systemic treatment in the past 2 years (ie, use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment. 14) Prior allogeneic tissue/solid organ transplant.

	15) History of (noninfectious) pneumonitis that required steroids or current pneumonitis. 16) Active, uncontrolled infection or infection requiring systemic therapy within ≤ 7 days of study entry. 17) Live vaccine within 30 days of start of study treatment. 18) Current participation in another interventional clinical study. 19) Known inherited or acquired bleeding disorders. 20) 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. 21) 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 5 years. 22) In patients with known history of HIV, presence of detectable viral load. HIV testing will be performed at screening only if required by local guidelines or institutional standards. 23) Known positivity for hepatitis B or C infection. Patients not currently on antiviral therapy and who have an undetectable viral load in the prior 3 months may be eligible for the study. Hepatitis B or C testing is not required. Patients with serologic evidence of prior vaccination to hepatitis B virus (ie, hepatitis B surface antigen negative and antibody against hepatitis B surface antigen positive) may participate. <u>Safety Run-in 1, Pre-expansion Safety Run-in for Magrolimab + Pembrolizumab (if Applicable), and Phase 2 Cohorts 1 and 2</u> 24) Progressive disease within 6 months of completion of curatively intended treatment for locoregionally advanced HNSCC. 25) Prior treatment with any of the following: a) Anti–programmed cell death protein 1 or anti–PD-L1 checkpoint inhibitors. b) Anti–cytotoxic T-lymphocyte–associated protein 4 checkpoint inhibitors. <u>Safety Run-in 2 and Phase 2 Cohort 3</u> 26) Progressive disease within 6 months of completion of curatively intended treatment for locally advanced/mHNSCC. 27) Prior treatment with a taxane.

Study Procedures/ Frequency:

In Safety Run-in 1, all eligible patients will receive magrolimab + pembrolizumab + platinum + 5-FU. In Phase 2 Cohort 1, eligible patients will be randomized in a 1:1 ratio to receive either magrolimab + pembrolizumab + platinum + 5-FU (Arm A) or pembrolizumab + platinum + 5-FU (Arm B). For platinum usage, cisplatin or carboplatin will be used per investigator choice. Study treatments are summarized below.

Safety Run-in 1: Dose De-escalation

Dose Level	Drug/Dose/Route	Dose Schedule (Day per 21-Day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
Starting dose	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 30 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 60 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1
	5-FU 1000 mg/m^2/day continuous IV	Days 1-4	Days 1-4	Days 1-4 Cycles 3-6
	Cisplatin 100 mg/m^2 IV (1 h) or Carboplatin AUC 5 IV (1 h)	Day 1	Day 1	Day 1 Cycles 3-6
Level minus 1	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 20 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 45 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1
	5-FU 1000 mg/m^2/day continuous IV	Days 1-4	Days 1-4	Days 1-4 Cycles 3-6
	Cisplatin 100 mg/m^2 IV (1 h) or Carboplatin AUC 5 IV (1 h)	Day 1	Day 1	Day 1 Cycles 3-6
Level minus 2	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 15 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 30 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1
	5-FU 1000 mg/m^2/day continuous IV	Days 1-4	Days 1-4	Days 1-4 Cycles 3-6
	Cisplatin 100 mg/m^2 IV (1 h) or Carboplatin AUC 5 IV (1 h)	Day 1	Day 1	Day 1 Cycles 3-6

5-FU = 5-fluorouracil; IV = intravenous

Phase 2 Cohort 1: Dose Level and Schedule

Treatment Group	Drug/Dose/Route	Dose Schedule (Day per 21-Day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
Arm A: Magrolimab + pembrolizumab + platinum + 5-FU	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab[a] IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab[a] IV (2 h ± 30 min)	—	—	Day 1
	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1
	5-FU 1000 mg/m^2/day continuous IV	Days 1-4	Days 1-4	Days 1-4 Cycles 3-6
	Cisplatin 100 mg/m^2 IV (1 h) or Carboplatin AUC 5 IV (1 h)	Day 1	Day 1	Day 1 Cycles 3-6
Arm B: Pembrolizumab + platinum + 5-FU	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1
	5-FU 1000 mg/m^2/day continuous IV	Days 1-4	Days 1-4	Days 1-4 Cycles 3-6
	Cisplatin 100 mg/m^2 IV (1 h) or Carboplatin AUC 5 IV (1 h)	Day 1	Day 1	Day 1 Cycles 3-6
Arm C: Magrolimab + Zimberelimab + platinum + 5-FU	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab[a] IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab[a] IV (2 h ± 30 min)	—	—	Day 1
	Zimberelimab 360 mg IV (60 min ± 15 min)	Day 1	Day 1	Day 1
	5-FU 1000 mg/m^2/day continuous IV	Days 1-4	Days 1-4	Days 1-4 Cycles 3-6
	Cisplatin 100 mg/m^2 IV (1 h) or Carboplatin AUC 5 IV (1 h)	Day 1	Day 1	Day 1 Cycles 3-6

5-FU = 5-fluorouracil; IV = intravenous; RP2D = recommended Phase 2 dose
a RP2D as determined in Safety Run-in 1.

If the sponsor determines that additional dose finding for magrolimab + pembrolizumab is needed, an additional pre-expansion safety run-in evaluation may be performed. In the optional Phase 2 Cohort 2, all eligible patients will receive magrolimab + pembrolizumab. Study treatments are summarized below.

Pre-expansion Safety Run-in for Magrolimab + Pembrolizumab: Dose De-escalation

Dose Level	Drug/Dose/Route	Dose Schedule (Day per 21-Day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
Starting dose	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 30 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 60 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1
Level minus 1	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 20 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 45 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1
Level minus 2	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 15 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 30 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1

IV = intravenous

Phase 2 Cohort 2: Dose Level and Schedule

Treatment Group	Drug/Dose/Route	Dose Schedule (Day per 21-Day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
Magrolimab + pembrolizumab	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab[a] IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab[a] IV (2 h ± 30 min)	—	—	Day 1
	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1

IV = intravenous; RP2D = recommended Phase 2 dose
a RP2D as determined in the pre-expansion safety run-in for magrolimab + pembrolizumab (if applicable).

In the Safety Run-in 2 and Phase 2 Cohort 3, all eligible patients will receive magrolimab + docetaxel. Study treatments are summarized below.

Safety Run-in 2: Dose De-escalation

Dose Level	Drug/Dose/Route	Dose Schedule (Day per 21-Day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
Starting dose	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 30 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 60 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Docetaxel 75 mg/m^2 IV (1 h ± 5 min)	Day 1	Day 1	Day 1
Level minus 1	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 20 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 45 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Docetaxel 75 mg/m^2 IV (1 h ± 5 min)	Day 1	Day 1	Day 1
Level minus 2	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 15 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 30 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Docetaxel 75 mg/m^2 IV (1 h ± 5 min)	Day 1	Day 1	Day 1

IV = intravenous

Phase 2 Cohort 3: Dose Level and Schedule

Treatment Group	Drug/Dose/Route	Dose Schedule (Day per 21-Day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
Magrolimab + docetaxel	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab[a] IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab[a] IV (2 h ± 30 min)	—	—	Day 1
	Docetaxel 75 mg/m^2 IV (1 h ± 5 min)	Day 1	Day 1	Day 1

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

Test Product, Dose, and Mode of Administration:	Safety Run-in 1 Starting Doses: • Magrolimab 1 mg/kg intravenous (IV) (priming dose) • Magrolimab 30 mg/kg IV • Magrolimab 60 mg/kg IV In combination with: • Pembrolizumab 200 mg IV • 5-FU 1000 mg/m^2/day continuous IV • Cisplatin 100 mg/m^2 IV or carboplatin AUC 5 IV Phase 2 Cohort 1: RP2D of magrolimab as determined in Safety Run-in 1 In combination with: • Pembrolizumab 200 mg IV • 5-FU 1000 mg/m^2/day continuous IV • Cisplatin 100 mg/m^2 IV or carboplatin AUC 5 IV • Zimberelimab 360 mg IV Phase 2 Cohort 2: RP2D based upon the pre-expansion safety run-in for magrolimab + pembrolizumab if applicable) In combination with pembrolizumab 200 mg IV Safety Run-in 2 Starting Doses: • Magrolimab 1 mg/kg IV (priming dose) • Magrolimab 30 mg/kg IV • Magrolimab 60 mg/kg IV In combination with docetaxel 75 mg/m^2 IV Phase 2 Cohort 3: • RP2D of magrolimab as determined in Safety Run-in 2.
Reference Therapy, Dose, and Mode of Administration:	Phase 2 Cohort 1: • Pembrolizumab 200 mg IV • 5-FU 1000 mg/m^2/day continuous IV • Cisplatin 100 mg/m^2 IV or carboplatin AUC 5 IV Optional Phase 2 Cohort 2: • Pembrolizumab 200 mg IV Phase 2 Cohort 3: • Docetaxel 75 mg/m^2 IV

Criteria for Evaluation:	
Safety:	Safety will be evaluated by data including the incidence of AEs for the duration of the study, assessment of clinical laboratory test findings, physical examinations, 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, OS, and PRO assessment (EORTC-QLQ-C30, EORTC QLQ-H&N35, and EQ-5D-5L) scores. For Phase 2 Cohort 1, the primary efficacy endpoint will be PFS as determined by investigator assessment. For Phase 2 Cohorts 2 and 3, assessment of response will be measured by RECIST, Version 1.1, as determined by investigator assessment (primary efficacy endpoint).
Pharmacokinetics:	For patients who receive magrolimab treatment, magrolimab serum drug concentrations will be assessed at predose at multiple time points until study discontinuation. Peripheral blood for immunogenicity assessments for ADAs against magrolimab will also be collected at predose at multiple time points during the study. Pharmacokinetic and ADA samples will also be collected and analyzed for patients who receive zimberelimab.
Statistical Methods:	<u>Analysis Data Sets</u> For the safety run-in evaluations, the DLT-Evaluable Analysis Set will include all enrolled patients who meet either of the following criteria during the DLT assessment period: • The patient experiences a DLT at any time after initiation of the first infusion of magrolimab. • The patient does not experience a DLT and completes at least 2 infusions of magrolimab and at least 1 dose of pembrolizumab, 1 dose of 5-FU, and 1 dose of platinum for Safety Run-in 1; at least 1 dose of docetaxel for Safety Run-in 2; and at least 1 dose of pembrolizumab for the pre-expansion safety run-in for magrolimab + pembrolizumab (if applicable). For the safety run-in evaluations, the Modified Intent-to-Treat and Safety Analysis Set will include all patients who receive at least 1 dose of any study drug.

	For the Phase 2 Cohort 1 randomized comparisons, the Intent-to-Treat Analysis Set will include all randomized patients according to the treatment group to which the patients are assigned, unless otherwise specified. The Safety Analysis Set will include all randomized patients who receive at least 1 dose of any study drug, with treatment assignment designated according to the actual treatment received. For Phase 2 Cohorts 2 and 3, the Modified Intent-to-Treat and Safety Analysis Sets will include all patients who receive at least 1 dose of any study drug. The PK Analysis Set will include all patients who receive any amount of magrolimab or zimberelimab and have at least 1 measurable posttreatment serum concentration of magrolimab or zimberelimab. The Immunogenicity Analysis Set will include all patients who receive any amount of magrolimab or zimberelimab and have at least 1 evaluable anti-magrolimab or anti-zimberelimab antibody test result. The Biomarker Analysis Set will include all patients who receive any study drug and have at least 1 evaluable biomarker measurement available. <u>Dose Determination Analysis</u> For the purposes of making the dose de-escalation decisions for the safety run-in evaluations, 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 1 dosing cycle (21 days). <u>Efficacy Analysis</u> For Phase 2 Cohort 1, PFS will be analyzed using Kaplan-Meier (KM) methods. Patients who do not have documented disease progression or death will be censored at the date of their last response assessment during the study with documentation of no disease progression. The KM estimate of the survival function will be computed, and the results will be presented using KM curves. The median will be provided along with the corresponding 95% CI. A log-rank test stratified by the randomization factors will be used to compare treatment difference in PFS. A stratified Cox proportional hazard regression model will be used to estimate the hazard ratio (HR) and its 2-sided 95% CI. For Phase 2 Cohorts 2 and 3, the ORR along with the 95% CI based on the Clopper-Pearson method will be estimated. Patients who do not have sufficient baseline or on-study tumor assessments to characterize response will be counted as nonresponders. <u>Safety Analysis</u> 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 Arm A versus Arm B, a total of 93 PFS events provides 75% power at a 1-sided alpha of 0.15 to detect an HR of 0.7 (assuming median PFS of 7 months compared with a control group median PFS of 4.9 months) using an unstratified log-rank test. Assuming an accrual period of 15 months, a minimum follow-up time of 5 months, and a 10% annual drop-out rate, 66 patients per treatment group (Arm A versus Arm B) would be required to obtain 93 events. Once the Phase 2 Cohort 1 enrolls 20 patients in each Arm A and Arm B, Arm C will open. For Arm C versus Arm B, a total of 61 PFS events provides 64% power at a 1-sided alpha of 0.15 to detect an HR of 0.7 (assuming a median PFS of 7 months compared with a control group median PFS of 4.9 months) using an unstratified log-rank test. Assuming an approximate accrual of 11 months, a minimum follow-up time of 5 months, and a 10% annual drop-out rate, 46 patients per treatment arm (Arm C versus concurrent Arm B) would be required to obtain 61 events. The control group assumption is based on pembrolizumab + platinum + 5-FU efficacy in a historical study (KEYNOTE-048). The power calculation was performed using EAST 6.5. For Phase 2 Cohort 2, no formal sample size calculation has been performed (25 patients). For Phase 2 Cohort 3, a sample size of 40 patients provides 83% power at a 1-sided alpha of 0.15 to detect an ORR of 18% compared with a null ORR of 7.9% using a chi-squared test. The null ORR is based on historical taxane efficacy data in the second-line setting. The power calculation was performed using 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

5-FU	5-fluorouracil
ABO	any of the 4 blood groups A, B, AB, and O comprising the ABO system
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_{tau}	area under the concentration versus time curve over the dosing interval
AxMP	auxiliary medicinal product
CD47	clusters of differentiation 47
CFR	Code of Federal Regulations
CI	confidence interval
C_{min}	minimum observed concentration of study drug
CMV	cytomegalovirus
CNS	central nervous system
CPS	combined positive score
CR	complete response
CRC	colorectal cancer
CRF	case report form
CSCO	Chinese Society of Clinical Oncology
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAT	direct antiglobulin test
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DPD	dihydropyrimidine dehydrogenase
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire
EORTC QLQ-H&N35	European Organisation for Research and Treatment of Cancer Quality of Life - Head and Neck Module
EQ-5D-5L	5-level EuroQol 5 dimensions
EQ-VAS	EuroQol visual analogue scale
EU	European Union

Fc	fragment crystallizable
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
Gilead	Gilead Sciences
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
HR	hazard ratio
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IgG4	immunoglobulin G4
IND	investigational new drug
IRB	institutional review board
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IRR	infusion-related reaction
IRT	interactive response technology
ITT	intent to treat
IV	intravenous
K_d	dissociation constant
KM	Kaplan-Meier
mAb	monoclonal antibody
MDS	myelodysplastic syndrome
mHNSCC	metastatic head and neck squamous cell carcinoma
mITT	modified intent to treat
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
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)
PR	partial response

PRO	patient-reported outcome
PS	Patient Safety
PT	prothrombin time
PTT	partial thromboplastin time
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
SD	standard deviation
SIRPα	signal regulatory protein alpha
SOP	standard operating procedure
SRT	Safety Review Team
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
ULN	upper limit of normal
US, USA	United States, United States of America
w/v	weight-to-volume ratio

1. INTRODUCTION

1.1. Background

1.1.1. Background on Head and Neck Squamous Cell Carcinoma

In the United States (US), head and neck cancers account for approximately 4% of all cancers. The annual incidence in the US is approximately 60,000 new cases, with approximately 14,000 deaths. Several risk factors are associated with the incidence of head and neck cancers, including tobacco and alcohol consumption. In addition, human papillomavirus (HPV) infection is a causative agent for head and neck cancers. Squamous cell carcinomas account for over 90% of head and neck cancers arising in the oral cavity and larynx. Initial treatment of head and neck squamous cell carcinoma (HNSCC) is broken down by extent of disease (localized, locoregionally advanced, and metastatic). Patients with localized disease (stage I or II) have a 5-year overall survival (OS) of 70% to 90% and are treated with definitive surgery and/or radiation therapy. In contrast, patients with metastatic disease have a poor prognosis, with a 5-year OS of approximately 4% {Beckham 2019}. Systemic therapy with either chemotherapy and/or immune checkpoint inhibition is the standard-of-care for patients with recurrent or metastatic disease in the frontline setting.

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

Patients who progress after initial immune checkpoint inhibitor therapy and/or chemotherapy are treated with taxanes, with a median progression-free survival (PFS) of 2.2 months and a median OS of 6.1 months {Siano 2017}. Patients with metastatic disease have a poor prognosis with limited tumor response. There is a significant unmet medical need in this patient population.

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 G4 (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 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).

According to 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 of 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 dissociation constant (K_d) of 8×10^{-9} and 8×10^{-12} M, respectively. Magrolimab bound to cynomolgus monkey and human CD47 with high affinity of K_d = 10 and 8.0 pM, respectively, but did not bind to mouse CD47. No complement-dependent cytotoxicity activity of magrolimab was observed in AML cells, and no antibody-dependent cellular 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. Moreover, the combination of magrolimab with cytotoxic agent azacitidine at a clinically relevant concentration enhanced phagocytosis of HL60 cells in vitro when compared with magrolimab or azacitidine alone. The combination of magrolimab and avelumab effectively enhanced phagocytosis of ovarian cancer cells by human macrophages compared with magrolimab or avelumab 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 in a variety of nonclinical cancer models, 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 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 red cell mass associated with decreases in mean corpuscular volume and haptoglobin; increases in mean corpuscular hemoglobin concentration, reticulocytes, and red cell distribution width; red cell 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 with the exception of increased spleen weights in males and females at 50 and 100 mg/kg at recovery necropsy, which had no macroscopic or microscopic correlate. Based on these results, the highest nonseverely toxic dose for this study was considered to be 100 mg/kg, the highest dose evaluated.

Reproductive and developmental toxicology studies have not been conducted by the sponsor, but all the available data (literature, data from knock-out 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 tumors. In this study, patients were treated with weekly magrolimab doses ranging from 0.1 to 45 mg/kg, with increasing serum concentrations associated with increasing dose. Nonlinear PK consistent with target-mediated clearance was observed over this dose range.

However, at maintenance doses of 10 mg/kg and above, target-mediated clearance was saturated within the dosing regimen, and trough levels associated with magrolimab efficacy in nonclinical studies were achieved. Nine of 88 evaluable patients (10%) 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 the 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 evaluable patients (15%) 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 patients (11%) 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.

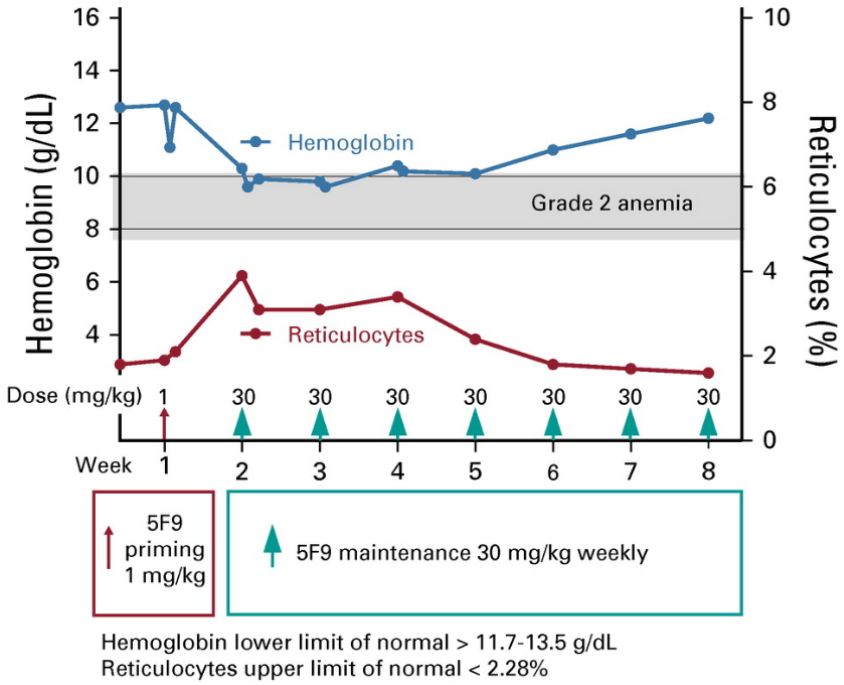
1.2.3.2. Summary of Clinical Safety

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 relapsed/refractory AML, along with 2 Phase 1b partnered studies in AML as well as urothelial carcinoma. Four combination studies include the following: Study 5F9003, a Phase 1b/2 study of magrolimab with rituximab in patients with relapsed/refractory NHL; Study 5F9004, a Phase 1b/2 study of magrolimab with cetuximab in patients with solid tumors and CRC; Study 5F9005, a Phase 1b study of magrolimab with azacitidine in patients with AML and MDS; and Study 5F9006, a Phase 1b study of magrolimab with avelumab in patients with solid tumors and ovarian cancer. As of July 2020, over 500 patients have been treated with magrolimab. Overall, the safety profile has been acceptable with magrolimab as monotherapy or in combination, with no maximum tolerated dose (MTD) reached in any study with dosing up to 45 mg/kg. Two anticipated adverse reactions included on-target anemia and infusion-related reactions (IRRs), which are expected with mAbs. Importantly, on-target anemia due to CD47 blockade-mediated RBC clearance was mitigated with a priming/maintenance dose strategy. The average hemoglobin decline with the first (priming) dose was 0.4 g/dL, with many patients improving their hemoglobin on therapy with a decrease in RBC transfusion requirements.

Magrolimab has been evaluated as a monotherapy or in combination in multiple solid tumor types. In a Phase 1 study of magrolimab monotherapy (Study SCI-CD47-001), 88 patients with advanced solid tumors and lymphomas were treated with magrolimab doses up to 45 mg/kg. No MTD was reached. Among the 548 patients with solid tumors or hematologic malignancies who were treated with magrolimab, fatigue, anemia, and headache were the 3 most frequently reported all-grade AEs (43.0%, 40.8%, and 36.4% of patients, respectively).

Anemia was the most common treatment-related AE, reported in 35.4% of patients. Approximately 13% of patients had Grade 1 or 2 anemia, and 22% of patients had severe anemia. Many of the AEs of severe anemia occurred in patients with AML and MDS who had 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 was 0.5 to 2 g/dL on average. In patients with solid tumors, the decrease 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 (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



5F9 = magrolimab (GS-4721)
The red blood cell profile of a patient with solid tumors who was 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. The most common signs/symptoms of IRR 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 Section 5.9.2. 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 patients with solid tumors/lymphoma and 222 patients with AML/MDS) 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 solid tumor and hematologic malignancies. In the Phase 1 study of magrolimab monotherapy in advanced solid tumors (Study SCI-CD47-001), 2 of 16 patients (12.5%) with clear cell ovarian and fallopian tube carcinomas achieved a partial response (PR) 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 patients with relapsed/refractory CRC (Study 5F9004), 2 objective responses out of 32 patients (6%) were observed in patients with relapsed/refractory metastatic KRAS wild-type CRC who were refractory to cetuximab with a disease control rate of 50% {Fisher 2020}. The OS in patients with KRAS wild-type and KRAS-mutant CRC treated with magrolimab and cetuximab was 9.5 and 7.6 months, respectively. These data may compare favorably to historical data in patients with KRAS wild-type and KRAS-mutant CRC treated with standard of care, where a median OS of 8.0 and 6.5 months, respectively, was observed {Van Cutsem 2018}.

In hematologic malignancies, efficacy has been observed in NHL, MDS, and AML. In Study 5F9003, patients with relapsed/refractory NHL were treated with magrolimab in combination with rituximab. Among 97 patients with NHL who were evaluable for efficacy, which included patients with diffuse large B-cell lymphoma (DLBCL) and indolent lymphoma, the objective response rate (ORR) was 45%, with a complete response (CR) rate of 19% {Advani 2019}. The ORR was 36% in 59 treated patients with DLBCL and 61% in 38 treated patients with indolent lymphoma. In Study 5F9005, patients with untreated AML who were ineligible for induction chemotherapy and patients with untreated higher-risk MDS were treated with magrolimab in combination with azacitidine. In 25 patients with AML, the ORR was 64% and the CR rate was 40% {Sallman 2020}. In 33 patients with MDS, the ORR was 91% and the CR rate was 42%. No median duration of response (DOR) was reached for either cohort, with median follow-up period of 9.4 months for AML and 5.8 months for MDS.

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

1.3. Information About Pembrolizumab, Zimberelimab, 5-Fluorouracil, Platinum (Cisplatin or Carboplatin), and Docetaxel

1.3.1. Description of Pembrolizumab

Pembrolizumab is a humanized IgG4 mAb with a high specificity of binding to the PD-1 receptor, inhibiting its interaction with PD-L1 and programmed cell death ligand 2. Pembrolizumab is indicated for the treatment of patients across a number of indications, including HNSCC, as a monotherapy in patients whose tumors express PD-L1 (CPS $\geq$ 1) and in combination with 5-FU and platinum chemotherapy regardless of PD-L1 status.

Further information can be found in the current country-specific prescribing information.

1.3.2. Description of Zimberelimab

Zimberelimab is a fully human IgG4 mAb targeting human PD-1. Zimberelimab, which is under development by Arcus Biosciences in partnership with Gilead Sciences, was generated by WuXi Biologics using the genetically engineered OmniRat platform, which was developed by Open Monoclonal Technology Company. Zimberelimab comprises 2 heavy chains of the IgG4 subclass and 2 light chains of the lambda subclass. The 4 chains are stabilized by multiple disulfide bonds, with a single glycosylation site (Asn300) located on the heavy chain. The molecular weight of zimberelimab is 144 kDa (deglycosylated mass), and its isoelectric point is 7.0.

1.3.3. Description of 5-Fluorouracil

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

Further information can be found in the current country-specific prescribing information.

1.3.4. Description of Cisplatin

Cisplatin is a platinum-based chemotherapy drug indicated for the treatment of multiple solid tumors including testicular, ovarian, and bladder cancer. It is also widely used for the treatment of other solid tumors, including HNSCC, lung, and cervical cancer.

Further information can be found in the current country-specific prescribing information.

1.3.5. Description of Carboplatin

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

Further information can be found in the current country-specific prescribing information.

1.3.6. Description of Docetaxel

Docetaxel is an anticancer chemotherapy drug classified as an antimicrotubule inhibitor and taxane. Docetaxel is indicated for multiple solid tumors, including HNSCC.

Further information can be found in the current country-specific prescribing information.

1.3.7. Clinical Data for Pembrolizumab

Pembrolizumab is indicated for the treatment of multiple solid tumors, including as a monotherapy for the first-line treatment of patients with metastatic or unresectable, recurrent HNSCC whose tumors express PD-L1 (CPS ≥ 1) {KEYTRUDA 2020a, KEYTRUDA 2020b}.

The approval of pembrolizumab monotherapy in HNSCC was based on results from the KEYNOTE-048 study, in which a total of 882 patients were enrolled. Treatment with pembrolizumab monotherapy resulted in an improved median OS compared with cetuximab + 5-FU + platinum in the subgroup of patients with a PD-L1 CPS ≥ 1 (12.3 months versus 10.3 months, respectively; HR: 0.78; $P = 0.0086$) and in the subgroup of patients with a PD-L1 CPS ≥ 20 (14.9 months versus 10.7 months; HR: 0.61; $P = 0.0007$) {Burtness 2019}. The median PFS in the pembrolizumab monotherapy group compared with the cetuximab + 5-FU + platinum group was 3.2 months versus 5.0 months, respectively, in the subgroup of patients with a PD-L1 CPS ≥ 1 and 3.4 months versus 5.0 months, respectively, in the subgroup of patients with a PD-L1 CPS ≥ 20. The ORR in the pembrolizumab monotherapy group compared with the cetuximab + 5-FU + platinum group was 19% versus 35%, respectively, in the subgroup of patients with a PD-L1 CPS ≥ 1 and 23% versus 36%, respectively, in the subgroup of patients with a PD-L1 CPS ≥ 20.

The most common AEs (≥ 10%) included fatigue, constipation, rash, nausea, diarrhea, vomiting, dyspnea, cough, hypothyroidism, decreased appetite, weight loss, pyrexia, pneumonia, headache, myalgia, and pruritus {KEYTRUDA 2020a, KEYTRUDA 2020b}. Pembrolizumab can cause severe or life-threatening IRRs including hypersensitivity and anaphylaxis, which have been reported in 6 of 2799 patients (0.2%) receiving pembrolizumab. Pembrolizumab can also cause immune-mediated reactions, some of which may be severe or fatal. Immune-mediated reactions include pneumonitis, colitis, hepatitis, adrenal insufficiency, hypophysitis, thyroid disorders, type 1 diabetes mellitus, and skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. Other immune-mediated reactions have also been observed with pembrolizumab and other PD-1/PD-L1 blocking antibodies, and they may also occur after discontinuation of treatment. Grade 3 or 4 laboratory abnormalities that worsened from baseline in ≥ 20% of patients included lymphopenia.

In summary, pembrolizumab monotherapy is an effective treatment option for the first-line treatment of patients with metastatic or unresectable, recurrent HNSCC whose tumors express PD-L1 (CPS ≥ 1).

1.3.8. Clinical Data for Zimberelimab

To date, 260 patients have been treated with zimberelimab in ongoing clinical studies sponsored by Arcus Biosciences.

At 360 mg every 3 weeks, mean area under the concentration-time curve to the end of the dosing period and minimum concentration were 21,000 ± 3780 µg•h/mL and 17.9 ± 6.27 µg/mL, respectively. Overall, the observed exposures were well below those reached in a 4-week toxicity study in cynomolgus monkeys.

Gloria Biosciences reported at the Chinese Society of Clinical Oncology (CSCO) in August 2019 (abstract available on request) that zimberelimab monotherapy has been evaluated in China in a Phase 1a/1b study (NCT03713905) in 220 patients with advanced relapsed/refractory solid tumors or lymphoma. These patients displayed multiple tumor types, including 35 patients with relapsed non-small-cell lung cancer (NSCLC). In these patients, the ORR was 25.7%, with a median duration of treatment of less than 4 months. Over the course of this study, no dose-limiting toxicity (DLT) has been reported and enrollment continues.

Encouraging data from 2 Phase 2 trials of zimberelimab monotherapy were presented at the American Society of Clinical Oncology Annual Meeting 2020. In a study of 44 patients with recurrent or metastatic PD-L1 positive (CPS > 1) cervical cancer (NCT03972722), zimberelimab was reported to have a manageable safety profile with an ORR of 28% {Wu 2020}. Additionally, in a study of 85 patients with relapsed or refractory classical Hodgkin's lymphoma (NCT03655483), zimberelimab demonstrated a manageable safety profile, and 91.8% of patients had a confirmed objective response, as assessed by an independent review committee, including 30 patients (35.3%) with CR and 48 patients (56.5%) with PR. Median DOR and PFS were not yet reached {Lin 2021}.

The most common AEs (≥ 10%) include fatigue, anemia, nausea, constipation, diarrhea, decreased appetite, pyrexia, neutrophil count decreased, dyspnea, alanine aminotransferase increased, aspartate aminotransferase increased, and headache (IB, V6).

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

1.3.9. Clinical Data for Pembrolizumab in Combination With 5-Fluorouracil and Platinum (Cisplatin or Carboplatin) Chemotherapy

Pembrolizumab in combination with 5-FU and platinum chemotherapy is indicated for the first-line treatment of patients with metastatic or unresectable, recurrent HNSCC regardless of PD-L1 status {KEYTRUDA 2020a, KEYTRUDA 2020b}.

Results from the KEYNOTE-048 study also led to the approval of the combination therapy in HNSCC. In the overall study population, regardless of PD-L1 status, treatment with pembrolizumab + 5-FU + platinum resulted in an improved median OS compared with cetuximab + 5-FU + platinum (13.0 months versus 10.7 months; HR: 0.77; $P = 0.0034$) {Burtness 2019}. The median PFS in the pembrolizumab + 5-FU + platinum group compared with the cetuximab + 5-FU + platinum group was 4.9 months versus 5.1 months, respectively. In both the pembrolizumab + 5-FU + platinum and cetuximab + 5-FU + platinum groups, the ORR was 36%.

The most common AEs (≥ 20%) included fatigue, mucosal inflammation, constipation, nausea, diarrhea, vomiting, stomatitis, cough, and decreased appetite {KEYTRUDA 2020a, KEYTRUDA 2020b}. Grade 3 or 4 laboratory abnormalities that worsened from baseline in ≥ 20% of patients included lymphopenia, anemia, neutropenia, and hyponatremia.

In summary, pembrolizumab in combination with 5-FU and platinum chemotherapy is an effective treatment option for the first-line treatment of patients with metastatic or unresectable, recurrent HNSCC regardless of PD-L1 status.

1.3.10. Clinical Data for Docetaxel

Docetaxel is approved for use in multiple solid tumors, including HNSCC {Taxotere® 1995, Taxotere® 1996}. Docetaxel is also widely used as standard of care in multiple solid tumors, including for the treatment of patients with HNSCC who fail first-line chemotherapy and/or immune checkpoint inhibitor therapy.

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. Docetaxel is contraindicated in patients with neutrophil counts < 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.

In general, the efficacy observed with docetaxel monotherapy in patients who fail standard chemotherapy, immune checkpoint inhibitor therapy, or the combination results in an ORR of approximately 7.9% in HNSCC {Cohen 2019, Ferris 2016}. The median PFS is approximately 7.4 weeks {Specenier 2011}.

1.3.11. Information on Study Auxiliary Medicinal Products/Noninvestigational Medicinal Products

Acetaminophen (also known as paracetamol), diphenhydramine, and dexamethasone are considered auxiliary medicinal products (AxMPs) for this clinical study (Appendix 13). 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 Section 5.9.2. Additional details on acetaminophen and diphenhydramine can be found in the prescribing information.

1.4. Rationale for This Study

Despite recent therapeutic improvements in the first-line mHNSCC setting, novel therapies and combinations are needed to extend survival benefit in this high unmet need population. Recently, the US Food and Drug Administration (FDA) approved pembrolizumab as a monotherapy in patients whose tumors express PD-L1 (CPS ≥ 1) and pembrolizumab in combination with 5-FU + platinum in patients regardless of PD-L1 tumor expression. These approvals were based on an approximately 2- to 3-month survival benefit in both settings, demonstrating the need for therapeutic combinations to improve patient benefit.

Magrolimab is a macrophage immune checkpoint inhibitor blocking CD47 that can activate both the innate and adaptive immune system through its unique mechanism of action. Several lines of evidence support the combination of magrolimab with T-cell checkpoint inhibitors with or without chemotherapy in patients with HNSCC. In syngeneic mouse models, CD47 blockade led to significant reduction in tumor growth {Wu 2018}. In a Phase 1 study of magrolimab monotherapy that included 4 patients with HNSCC (Study SCI-CD47-001), magrolimab was well tolerated and prolonged disease stabilization in several patients {Sikic 2019}. Strong scientific rationale and nonclinical data also support the combination of magrolimab with T-cell checkpoint inhibitors. Macrophage phagocytosis of tumor cells by CD47 blockade leads to cross-presentation of tumor antigens by macrophages to T cells, thus engaging a T-cell antitumor response {Tseng 2013}. Multiple nonclinical studies demonstrate that the addition of CD47 blockade to anti–PD-1/L1 checkpoint blockade enhances antitumor efficacy through stimulation of both innate and adaptive immune responses {Gordon 2017, Sockolosky 2016}. Thus, the combination of CD47 blockade and PD-1/PD-L1 T-cell checkpoint blockade is anticipated to enhance antitumor efficacy by combining both innate and adaptive immune responses. Indeed, multiple nonclinical studies have demonstrated enhancement of antitumor efficacy when an anti-CD47 antibody is combined with anti–PD-1/PD-L1 blockade in multiple solid tumor types {Lian 2019, Liu 2018, Wang 2020}. Magrolimab can also enhance the antitumor efficacy of chemotherapy by enhancing phagocytosis via upregulation of prophagocytic signals on tumor cells. Magrolimab in combination with chemotherapy led to substantial reduction of tumor growth in solid tumor xenograft models {Kiss 2020}. Furthermore, clinical studies evaluating magrolimab in combination with combination chemotherapy are ongoing. In an ongoing Phase 1b/2 study of magrolimab in combination with rituximab, gemcitabine, and oxaliplatin (Study 5F9003), the combination therapy has been well tolerated, with no MTD reached and patients being evaluated for preliminary efficacy in an expansion cohort.

To date, magrolimab has been evaluated in patients in combination with anti–PD-L1 inhibitors. Study 5F9006 evaluated magrolimab in combination with avelumab in relapsed/refractory ovarian cancer. An additional ongoing study (WO39613) is evaluating magrolimab in combination with atezolizumab in second-line bladder cancer. In both studies, magrolimab has been well tolerated with either avelumab or atezolizumab, with no MTD reached. In addition, no substantial enhancement of immune-activating AEs observed with T-cell checkpoint inhibitors was observed when magrolimab was added in combination (data on file).

Emerging clinical data with CD47 blockade in combination with pembrolizumab suggest potential activity in HNSCC. A combination of ALX148 (a CD47-blocking SIRPα-Fc fusion protein) with pembrolizumab in 10 patients with checkpoint inhibitor–naive relapsed/refractory HNSCC led to an ORR of 40% {Chow 2020}. In addition, ALX148 is also being evaluated in combination with pembrolizumab + 5-FU + platinum. Three of 4 patients (75%) treated with this combination achieved an objective response, with 1 patient achieving a CR {Lee 2020}. Furthermore, this CD47-blocking agent in combination with either pembrolizumab or pembrolizumab + chemotherapy was well tolerated, with no MTD reached. No significant safety signals were observed beyond what was expected from pembrolizumab or pembrolizumab in combination with chemotherapy, suggesting that CD47-targeting agents can be safely combined with these combinations. While patient numbers are limited, these data suggest potential meaningful combination activity of CD47 blockade and pembrolizumab compared with historical response rates of pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy in this setting.

In nonclinical models, zimberelimab was observed to be similar to the approved anti–PD-1 checkpoint inhibitor, pembrolizumab, with comparable interferon-gamma production in an allogenic model, distinct but overlapping PD-1 binding epitopes, and a higher kinetic affinity to PD-1. Additionally, based on clinical data in 39 patients, zimberelimab has pharmacodynamic ([PD]; increased proliferating Ki-67 positive T cells in blood), and PK properties comparable to approved PD-1 agents, pembrolizumab and nivolumab. Thus, zimberelimab has been included in Cohort 1 Arm C to investigate the combination potential with magrolimab, platinum, and 5-FU. For further information on zimberelimab, refer to the current IB.

In summary, the combined nonclinical rationale of magrolimab in combination with checkpoint inhibitors and/or chemotherapy, initial tolerability of magrolimab in patients with HNSCC, and emerging clinical efficacy of CD47 blockade with immune checkpoint inhibitors support the rationale for the proposed combinations in this study.

1.5. Rationale for Dose Selection

1.5.1. Magrolimab

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

In the first-in-human study of magrolimab (Study 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}. The maximum weekly dose of 45 mg/kg has an acceptable safety profile, and no MTD was identified in this study. In Studies 5F9004 (patients with solid tumors and CRC) and 5F9006 (patients with solid tumors and ovarian cancer), magrolimab, in combination with cetuximab and avelumab, respectively, was found to have an acceptable safety profile at doses up to 45 mg/kg every week followed by every other week.

In solid tumors where the combination therapy (chemotherapy or pembrolizumab/zimberelimab) 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 dose is predicted to provide a similar trough concentration and RO as the 30 mg/kg every 2 weeks dose, the dose being used in Phase 3 studies in AML and MDS. Updated PK modeling from the 5F9005 study showed that the magrolimab dose of 45 mg/kg every 3 weeks was suboptimal compared with 30 mg/kg every 2 weeks and 60 mg/kg every 3 weeks in maintaining similar trough concentration. Maintaining adequate trough concentration may be necessary for optimal efficacy considering that some patients may experience dose delays due to toxicity. Furthermore, the PK-PD modeling also indicates that at these extended interval dosing regimens, the RO will be maintained at maximal

levels (> 90%) in peripheral blood and tumor tissues. The proposed dosing regimen of magrolimab in this study is expected to have an acceptable safety profile based on the entirety of safety data in multiple oncology populations, both as a monotherapy and in combination with other tumor targeted antibodies and chemotherapeutics.

1.5.2. Zimberelimab

The dose and schedule of zimberelimab (360 mg every 3 weeks) to be evaluated in this study was determined based on preliminary PK, PD, and safety findings from the ongoing Phase 1 study of zimberelimab in patients with advanced solid tumors (AB122CSP0001). Refer to the Zimberelimab IB, Edition 6 for nonclinical results and preliminary clinical PK, PD, and safety results from Study AB122CSP0001.

In vitro studies with zimberelimab have indicated that serum concentrations in excess of approximately 1.5 µg/mL (corresponding to ~10 nM) would provide a maximal blockade of PD-1 (or RO) on blood T cells. The preliminary PK data available for zimberelimab from Study AB122CSP0001 indicate that, in the zimberelimab 240 mg every 2 weeks cohort (n = 6), a minimum concentration (C_{min}) of 15.3 ± 5.44 µg/mL (corresponding to approximately 105.9 ± 37.7 nM) was achieved. The mean AUC from 0 to 14 days (AUC_{tau}) for Cycle 1 Day 1 in this cohort (10,200 ± 2500 µg•h/mL) was comparable to the value of 8790 µg•h/mL reported for the approved anti–PD-1 agent nivolumab at the dose of 3 mg/kg every 2 weeks {Center for Drug Evaluation and Research (CDER) 2014}. In the zimberelimab 360 mg every 3 weeks cohort (n = 6), higher C_{min} and AUC_{tau} for Cycle 1 Day 1 were observed at 17.9 µg/mL and 21,000 µg•h/mL, respectively.

Dosing regimens of approved anti–PD-1 antibodies are associated with RO on peripheral blood T cells in excess of 65% {Topalian 2012}. While different assay formats have been used by different groups to quantify RO, at least 1 of the assays employed in Study AB122CSP0001 is similar to the one employed to describe the effects of nivolumab {Topalian 2012}. Consistent with the potency of zimberelimab in in vitro assays, a preliminary analysis of clinical samples from Study AB122CSP0001 confirmed that, in the 240-mg every 2 weeks cohort, ≥ 65% RO (defined using 2 different assays) was achieved at all measured time points, including in Cycle 1 Day 15 predose samples, when serum concentrations of zimberelimab were lowest, just prior to administration of the Cycle 1 Day 15 dose. The 360 mg every 3 weeks dosing regimen was evaluated in Study AB122CSP0001 (n = 6). Using 2 different assay methods, RO of ≥ 65% was achieved at the C_{min} time points evaluated.

The available PK and PD data support the maximal exposure and binding of zimberelimab at 360 mg every 3 weeks, which would allow for maximal clinical activity.

1.6. Risk/Benefit Assessment for the Study

First-line locally advanced or mHNSCC has a poor prognosis despite current therapies, with a median OS of approximately 10 to 12 months. Pembrolizumab is indicated for patients whose tumors express PD-L1 (CPS ≥ 1), whereas pembrolizumab in combination with 5-FU and platinum is indicated for patients regardless of PD-L1 status. The approvals of pembrolizumab as a monotherapy and in combination with chemotherapy were based on a median OS benefit of approximately 2 to 3 months over standard of care, underlying the great unmet needs of this

population. Therapies are needed that can enhance the activity of pembrolizumab as a monotherapy and in combination with chemotherapy in a manner that is well tolerated {Burtness 2019}.

Strong scientific and nonclinical data support the rationale for combining magrolimab with pembrolizumab or with pembrolizumab, 5-FU, and platinum. Multiple nonclinical in vivo models demonstrate improved efficacy with the addition of CD47 blockade to T-cell checkpoint inhibitors and/or chemotherapy. Furthermore, initial clinical data demonstrate an encouraging efficacy signal when CD47 blockade is combined with pembrolizumab in second-line checkpoint inhibitor–naive HNSCC {Chow 2020}. Specifically, in 10 patients, a 40% ORR was observed with pembrolizumab in combination with ALX148, a SIRPα-Fc fusion protein that blocks CD47. In addition, 3 of 4 patients (75%) treated with ALX148 in combination with pembrolizumab, 5-FU, and platinum achieved an objective response {Lee 2020}. While patient numbers are limited, these initial data suggest a potential efficacy benefit of the combination compared with pembrolizumab alone or pembrolizumab in combination with chemotherapy. In addition, magrolimab has shown combination efficacy when added with chemotherapeutic regimens, including platinum-containing chemotherapy. In an ongoing Phase 1b/2 study (5F9003), magrolimab in combination with rituximab, gemcitabine, and oxaliplatin was shown to be well tolerated and induced several objective responses, including complete remissions, in the Phase 1b dose-escalation phase. This study is now enrolling in the expansion phase. Thus, multiple lines of evidence support the therapeutic potential of magrolimab in combination with pembrolizumab, with and without 5-FU and platinum.

There are no significant, anticipated overlapping toxicities between magrolimab and pembrolizumab, with the exception of IRRs. Similarly, there are no significant, anticipated overlapping toxicities between magrolimab and zimberelimab (except IRRs). Infusion-related reactions are mitigated with several measures in this study, including close patient monitoring, premedications, and guidance regarding the treatment of IRR should it occur. Experience from other anti–PD-1 agents such as pembrolizumab can provide an understanding of potential risks. Immune-activating AEs have not been associated with magrolimab. In addition, 2 studies have evaluated magrolimab in combination with anti–PD-L1 antibodies (avelumab in ovarian cancer [Study 5F9006] and atezolizumab in bladder cancer and AML [Study WO39613]). The combinations of magrolimab with anti–PD-L1 antibodies (avelumab and atezolizumab) were generally well tolerated with no MTD reached in any study. Thus, the safety profile of magrolimab in combination with pembrolizumab is expected to be acceptable. The safety profile of magrolimab in combination with platinum + 5-FU or docetaxel is also expected to be acceptable with minimum overlapping toxicities. Anemia, neutropenia, thrombocytopenia, and infections have been reported in patients treated with magrolimab and are potential overlapping toxicities with platinum, 5-FU, and docetaxel in this study. However, these toxicities are mitigated with several measures, including a priming/maintenance dose strategy for magrolimab to mitigate on-target anemia and transfusion as needed, frequent complete blood counts to monitor neutrophil and platelet counts, and enrollment of patients with a hemoglobin level of at least 9 g/dL. Guidance for magrolimab dosing during episodes of neutropenia or infection is provided in Section 7.8.1.6 and Section 7.8.1.7, respectively. Magrolimab is currently being evaluated with other platinum-containing chemotherapeutic regimens (including a combination with rituximab, gemcitabine, and oxaliplatin in DLBCL). Magrolimab in combination with rituximab, gemcitabine, and oxaliplatin has been well tolerated, with no MTD reached. Overall,

magrolimab in combination with pembrolizumab with or without 5-FU and platinum chemotherapy, magrolimab in combination with zimberelimab with 5-FU and platinum chemotherapy, or magrolimab in combination with docetaxel is expected to have an acceptable safety profile.

During a pandemic, additional potential risks to patients may include adequate study drug availability, interruptions to the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 3 for further details on the risks and risk mitigation strategy.

In summary, based on strong scientific rationale, nonclinical, and emerging clinical data, lack of potential toxicities, and the risk mitigation measures being implemented for the pandemic, the evaluation of magrolimab in combination with pembrolizumab + platinum + 5-FU, magrolimab in combination with pembrolizumab, and magrolimab in combination with docetaxel in patients with HNSCC is anticipated to have an acceptable risk-benefit ratio for the patients enrolled in this study.

1.7. Compliance

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

2. OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are presented in Table 1. Analyses of the study endpoints are described in Section 8.

Table 1. Study Objectives and Endpoints

Primary Objectives	Primary Endpoints
Safety Run-in: • To evaluate the safety, tolerability, and RP2D of magrolimab in combination with the following: — Pembrolizumab + platinum + 5-FU — Docetaxel Phase 2 Cohorts: • To evaluate the PFS with magrolimab in combination with pembrolizumab + platinum + 5-FU versus pembrolizumab + platinum + 5-FU as determined by investigator assessment (Phase 2 Cohort 1) • To evaluate the efficacy of magrolimab in combination with pembrolizumab, if this optional cohort is opened, and magrolimab in combination with docetaxel as determined by the investigator-assessed ORR (Phase 2 Cohorts 2 and 3)	Safety Run-in: • Incidence of AEs and laboratory abnormalities defined as DLTs according to the NCI CTCAE, Version 5.0 (Appendix 4) Phase 2 Cohorts: • PFS, defined as the time from the date of randomization until the earliest date of documented disease progression, as determined by investigator assessment, or death from any cause, whichever occurs first (Phase 2 Cohort 1, Arm A versus Arm B) • ORR, defined as the proportion of patients who achieve a CR or PR as measured by RECIST, Version 1.1, as determined by investigator assessment (Phase 2 Cohorts 2 and 3)
Secondary Objectives	**Secondary Endpoints**
Safety Run-in: • To evaluate the PK and immunogenicity of magrolimab in combination with anticancer therapies Phase 2 Cohorts: • To evaluate PFS for magrolimab + zimberelimab + platinum + 5-FU versus pembrolizumab + platinum + 5-FU as determined by investigator assessment (Phase 2 Cohort 1) • To evaluate ORR as determined by investigator assessment (Phase 2 Cohort 1) • To evaluate PFS by investigator assessment (Phase 2 Cohorts 2 and 3) • To evaluate additional measures of efficacy, including DOR and OS • To evaluate the PK and immunogenicity of magrolimab in combination with anticancer therapies • To evaluate PROs/quality-of-life measures	Safety Run-in: • Magrolimab concentration versus time and ADAs to magrolimab Phase 2 Cohorts: • PFS, as determined by investigator assessment or death from any cause, whichever occurs first (Phase 2 Cohort 1, Arm C versus concurrent Arm B) • ORR, as determined by investigator assessment (Phase 2 Cohort 1) • PFS from date of dose initiation (Phase 2 Cohort 2 and Phase 2 Cohort 3) until the earliest date of documented disease progression as determined by investigator assessment per RECIST, Version 1.1, or death from any cause, whichever occurs first • DOR, defined as time from first documentation of CR or PR to the earliest date of documented disease progression or death from any cause, whichever occurs first • OS, defined as time from date of randomization (Phase 2 Cohort 1) or date of dose initiation (Phase 2 Cohort 2 and Phase 2 Cohort 3) to death from any cause

	• Magrolimab concentration versus time and ADAs to magrolimab • PRO assessment (EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D-5L) scores
CCI	

5-FU = 5-fluorouracil; ADA = antidrug antibody; AE = adverse event; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; DOR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire; EORTC QLQ-H&N35 = European Organisation for Research and Treatment of Cancer Quality of Life - Head and Neck Module; EQ-5D-5L = 5-level EuroQol 5 dimensions questionnaire; NCI = National Cancer Institute; ORR = objective response rate; OS = overall survival; PD = pharmacodynamic(s); PFS = progression-free survival; PK = pharmacokinetic(s); PR = partial response; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose

3. STUDY DESIGN

3.1. Study Design

This is a Phase 2, open-label, multicenter study evaluating magrolimab in combination with pembrolizumab + platinum + 5-FU chemotherapy; magrolimab in combination with pembrolizumab; magrolimab in combination with zimberelimab + platinum + 5-FU chemotherapy in patients with untreated metastatic or unresectable, locally recurrent HNSCC; and magrolimab in combination with docetaxel in patients with locally advanced/mHNSCC who were previously treated with at least 1 and no more than 2 lines of prior systemic therapy.

This study will consist of the following 2 safety run-in evaluations:

- **Safety Run-in 1:** magrolimab + pembrolizumab + platinum + 5-FU in patients with untreated metastatic or unresectable, locally recurrent HNSCC regardless of PD-L1 status
- **Safety Run-in 2:** magrolimab + docetaxel in patients with locally advanced/mHNSCC regardless of PD-L1 status who were previously treated with at least 1 and no more than 2 lines of prior systemic therapy

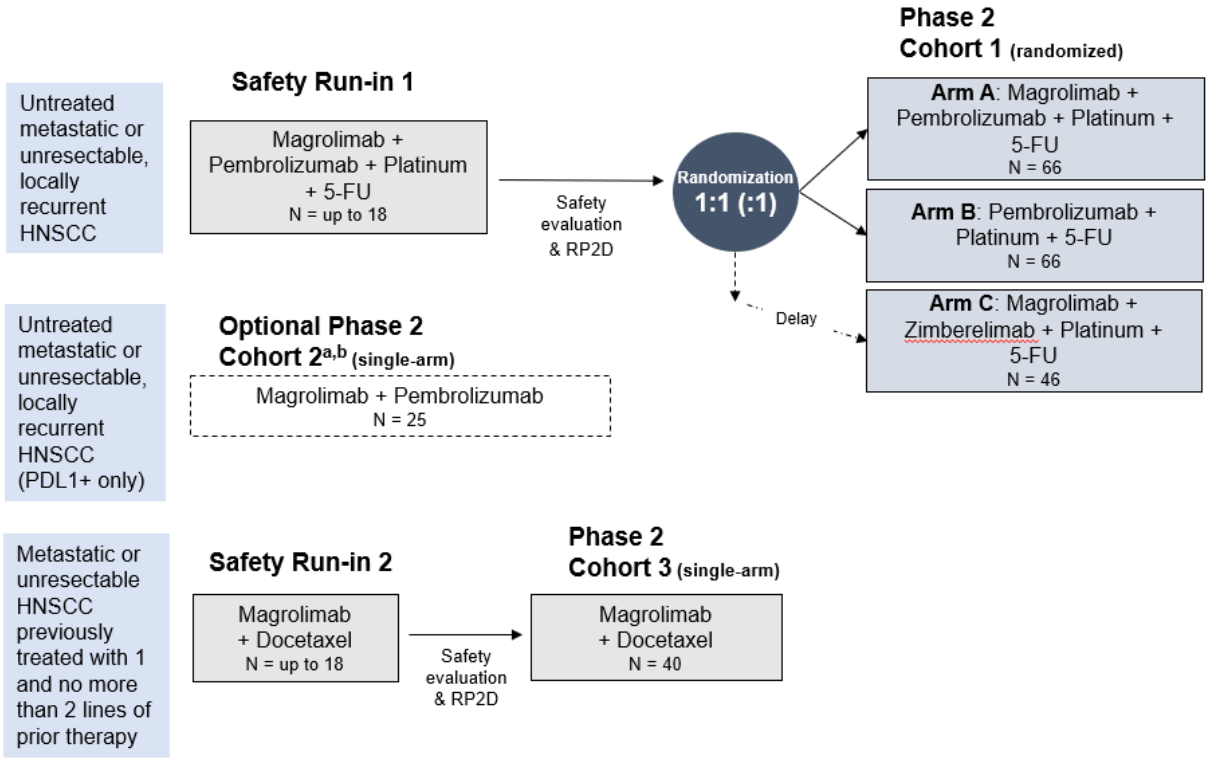
Additionally, a pre-expansion safety run-in evaluation of magrolimab + pembrolizumab in patients with untreated metastatic or unresectable, locally recurrent HNSCC with a PD-L1 CPS $\geq$ 1 may be conducted at the sponsor's discretion prior to the initiation of the optional Phase 2 Cohort 2 evaluating a single arm of magrolimab + pembrolizumab.

Once the Safety Review Team (SRT) reviews the safety for the patients in each run-in and the sponsor determines the recommended Phase 2 dose (RP2D) for that cohort, Phase 2 Cohorts 1 and 3 will be conducted, as described in Section 3.1.2.

Patient participation will include screening, randomization (Phase 2 Cohort 1 only), treatment, and follow-up. Screening will last up to 30 days before 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



5-FU = 5-fluorouracil; HNSCC = head and neck squamous cell carcinoma; PD-L1 = programmed cell death ligand 1; RP2D = recommended Phase 2 dose

a Optional cohort to be opened at the discretion of the sponsor.

b A pre-expansion safety run-in evaluation of magrolimab + pembrolizumab may be conducted at the sponsor's discretion prior to the initiation of this optional cohort.

3.1.1. Safety Run-in

3.1.1.1. Safety Run-in 1

A 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 (DLT definition is provided in Section 3.1.1.1.2).

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

- If no more than 2 of 6 DLT-evaluable patients experience a DLT in Cycle 1, enrollment into Phase 2 Cohorts 1 and 2 will begin at this dose level.

- If 3 or more (> 34%) DLT-evaluable patients experience a DLT at any time, another 6 patients will be enrolled at a lower dose and will be evaluated in the same manner to define the recommended dose for the combination regimen.

Dose de-escalation for Safety Run-in 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 SRT and sponsor.

3.1.1.1.1. Dose-Limiting Toxicity Assessment Period for Safety Run-in 1

The DLT assessment period will be the first cycle (21 days) and applies to Safety Run-in 1. Patients will be considered evaluable for assessment of DLTs if either of the following criteria is met during the DLT assessment period:

- The patient experiences a DLT at any time after initiation of the first infusion of magrolimab.
- The patient does not experience a DLT and completes at least 2 infusions of magrolimab and at least 1 dose of pembrolizumab, 1 dose of 5-FU, and 1 dose of platinum.

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 Safety Run-in 1 will be replaced.

Patients enrolled in Safety Run-in 1 will continue treatment until unacceptable toxicity or disease progression, whichever occurs first, and will not change their magrolimab dose level after the RP2D is determined.

3.1.1.1.2. Dose-Limiting Toxicity Definition for Safety Run-in 1

All toxicities will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (Appendix 4). A DLT is defined as an event meeting Hy's Law criteria (Section 7.7), any Grade 3 or higher hematologic toxicity or Grade 3 or higher nonhematologic toxicity that has worsened in severity from pretreatment baseline during the DLT assessment period and, in the opinion of the investigator, the AE is related to magrolimab and the relationship of the AE with the combination partner regimen can be ruled out.

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 life is considered a DLT.
- Grade 3 neutropenia that resolves to Grade 2 within 3 weeks with supportive care measures (ie, granulocyte colony-stimulating factor [G-CSF]) or Grade 4 neutropenia lasting for 7 days or less with supportive measures.

- Grade 3 thrombocytopenia in the absence of clinically significant bleeding that resolves to Grade 2 or pretreatment baseline within 3 weeks.
- 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.
- Isolated Grade 3 electrolyte abnormalities that resolve to ≤ Grade 2 with supportive care within 72 hours and are not associated with other clinically significant consequences.
- Grade 3 elevation in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) up to ≤ 8 × upper limit of normal (ULN) lasting < 7 days. Grade 3 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 with supportive care within 72 hours.
- Grade 3 fatigue that resolves to ≤ Grade 2 within 2 weeks on study.
- Grade 3 magrolimab, 5-FU, or platinum 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 hypomagnesemia that resolves 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.
- Tumor flare phenomenon, defined as local pain, irritation, or rash localized at sites of known or suspected tumor, that resolves within 72 hours with supportive care measures.
- Grade 3 lipase and/or amylase elevation without clinical or radiologic evidence of pancreatitis.

The RP2D will be determined by the sponsor based on all relevant clinical and PK data from all patients treated in Safety Run-in 1.

3.1.1.2. Safety Run-in 2

Safety Run-in 2 will open for enrollment at the same time as Safety Run-in 1. A 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 (DLT definition is provided in Section 3.1.1.2.1).

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

- If no more than 2 of 6 DLT-evaluable patients experience a DLT in Cycle 1, enrollment into Phase 2 Cohort 3 will begin at this dose level.

- If 3 or more (> 34%) DLT-evaluable patients experience a DLT at any time, another 6 patients will be enrolled at a lower dose and will be evaluated in the same manner to define the recommended dose for the combination regimen.

Dose de-escalation for Safety Run-in 2 is presented in Table 6. Based on the totality of the data, alternative doses of magrolimab not described in Table 6 may be considered for dose de-escalation by the SRT and sponsor.

3.1.1.2.1. Dose-Limiting Toxicity Assessment Period for Safety Run-in 2

The DLT assessment period will be the first cycle (21 days) and applies to Safety Run-in 2. Patients will be considered evaluable for assessment of DLTs if either of the following criteria is met during the DLT assessment period:

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

- The patient does not experience a DLT and completes at least 2 infusions of magrolimab and at least 1 dose of docetaxel.

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 Safety Run-in 2 will be replaced.

Patients enrolled in Safety Run-in 2 will continue treatment until unacceptable toxicity or disease progression, whichever occurs first, and will not change their magrolimab dose level after the RP2D is determined.

3.1.1.2.2. Dose-Limiting Toxicity Definition for Safety Run-in 2

All toxicities will be graded according to the NCI CTCAE, Version 5.0 (Appendix 4). A DLT is defined as an event meeting Hy's Law criteria (Section 7.7), any Grade 3 or higher hematologic toxicity or Grade 3 or higher nonhematologic toxicity that has worsened in severity from pretreatment baseline during the DLT assessment period and, in the opinion of the investigator, the AE is related to magrolimab and the relationship of the AE with the combination partner regimen can be ruled out.

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 life is considered a DLT.

- Grade 3 neutropenia that resolves to Grade 2 within 3 weeks with supportive care measures (ie, G-CSF) or Grade 4 neutropenia lasting for 7 days or less with supportive measures.

- Grade 3 thrombocytopenia in the absence of clinically significant bleeding that resolves to Grade 2 or pretreatment baseline within 3 weeks.
- 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.
- Isolated Grade 3 electrolyte abnormalities that resolve to ≤ Grade 2 with supportive care within 72 hours and are not associated with other clinically significant consequences.
- Grade 3 elevation in ALT and/or AST up to ≤ 8 × ULN lasting < 7 days. Grade 3 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 with supportive care within 72 hours.
- Grade 3 fatigue that resolves to ≤ Grade 2 within 2 weeks on study.
- Grade 3 magrolimab or 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 hypomagnesemia that resolves 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.
- Tumor flare phenomenon, defined as local pain, irritation, or rash localized at sites of known or suspected tumor, that resolves within 72 hours with supportive care measures.

The RP2D will be determined by the sponsor based on all relevant clinical and PK data from all patients treated in Safety Run-in 2.

3.1.1.3. Pre-expansion Safety Run-in for Magrolimab + Pembrolizumab

If the sponsor determines that additional dose finding for magrolimab + pembrolizumab is needed, 6 patients will be enrolled to receive magrolimab + pembrolizumab in this safety run-in evaluation. A DLT evaluation period of 1 cycle (21 days) will occur (DLT definition is provided in Section 3.1.1.3.2).

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

- If no more than 2 of 6 DLT-evaluable patients experience a DLT in Cycle 1, enrollment into Phase 2 Cohort 2 will begin at this dose level.

- If 3 or more (> 34%) DLT-evaluable patients experience a DLT at any time, another 6 patients will be enrolled at a lower dose and will be evaluated in the same manner to define the recommended dose for the combination regimen.

Dose de-escalation for the pre-expansion safety run-in evaluation for magrolimab + pembrolizumab is presented in Table 4.

3.1.1.3.1. Dose-Limiting Toxicity Assessment Period for the Pre-expansion Safety Run-in for Magrolimab + Pembrolizumab

The DLT assessment period will be the first cycle (21 days) and applies to this safety run-in evaluation. Patients will be considered evaluable for assessment of DLTs if either of the following criteria is met during the DLT assessment period:

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

- The patient does not experience a DLT and completes at least 2 infusions of magrolimab and at least 1 dose of pembrolizumab.

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 this safety run-in will be replaced.

Patients enrolled in this safety run-in evaluation will continue treatment until unacceptable toxicity or disease progression, whichever occurs first, and will not change their magrolimab dose level after the RP2D is determined.

3.1.1.3.2. Dose-Limiting Toxicity Definition for the Pre-expansion Safety Run-in for Magrolimab + Pembrolizumab

All toxicities will be graded according to the NCI CTCAE, Version 5.0 (Appendix 4). A DLT is defined as an event meeting Hy's Law criteria (Section 7.7), any Grade 3 or higher hematologic toxicity or Grade 3 or higher nonhematologic toxicity that has worsened in severity from pretreatment baseline during the DLT assessment period and, in the opinion of the investigator, the AE is related to magrolimab and the relationship of the AE with the combination partner regimen can be ruled out.

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 life is considered a DLT.

- Grade 3 neutropenia that resolves to Grade 2 within 3 weeks with supportive care measures (ie, G-CSF) or Grade 4 neutropenia lasting for 7 days or less with supportive measures.

- Grade 3 thrombocytopenia in the absence of clinically significant bleeding that resolves to Grade 2 or pretreatment baseline within 3 weeks.
- 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.
- Isolated Grade 3 electrolyte abnormalities that resolve to ≤ Grade 2 with supportive care within 72 hours and are not associated with other clinically significant consequences.
- Grade 3 elevation in ALT and/or AST up to ≤ 8 × the ULN lasting < 7 days. Grade 3 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 with supportive care within 72 hours.
- Grade 3 fatigue that resolves to ≤ Grade 2 within 2 weeks on study.
- Grade 3 magrolimab or pembrolizumab 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 hypomagnesemia that resolves 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.
- Tumor flare phenomenon, defined as local pain, irritation, or rash localized at sites of known or suspected tumor, that resolves within 72 hours with supportive care measures.
- Grade 3 lipase and/or amylase elevation without clinical or radiologic evidence of pancreatitis.

The RP2D will be determined by the sponsor based on all relevant clinical and PK data from all patients treated in this safety run-in.

3.1.1.4. 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, the Gilead Sciences (Gilead) medical monitor, and the Gilead Patient Safety (PS) physician. Others may be invited to participate as members of the SRT if additional expertise is desired (ie, representatives from Clinical Operations, Biostatistics,

Clinical Pharmacology, and Biomarker Sciences, as applicable). 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 dose de-escalation decisions will be defined in the SRT charter (or similar document). The quality control checks performed on the data reviewed and used for making decisions will be described in the SRT charter (or similar document).

3.1.2. Phase 2 Cohorts

Once the SRT reviews each safety run-in evaluation and the sponsor determines the RP2D for that study population, the following Phase 2 Cohorts will be conducted:

- **Phase 2 Cohort 1:** a randomized, open-label cohort of magrolimab + pembrolizumab + platinum + 5-FU (Arm A) versus pembrolizumab + platinum + 5-FU (Arm B) versus a delayed open arm magrolimab + zimberelimab + platinum + 5-FU (Arm C) in patients with untreated metastatic or unresectable, locally recurrent HNSCC regardless of PD-L1 status.

- **Phase 2 Cohort 2:** At the sponsor's discretion, a cohort of magrolimab + pembrolizumab in patients with untreated metastatic or unresectable, locally recurrent HNSCC with a PD-L1 CPS ≥ 1 may be opened.

- **Phase 2 Cohort 3:** a cohort of magrolimab + docetaxel in patients with locally advanced/mHNSCC regardless of PD-L1 status who were previously treated with at least 1 and no more than 2 lines of prior systemic therapy.

3.1.2.1. Phase 2 Cohort 1

Once the SRT reviews Safety Run-in 1 and the sponsor determines the RP2D for magrolimab + pembrolizumab + platinum + 5-FU, a Phase 2, randomized, open-label cohort with a 2-treatment-group design will open for enrollment. Approximately 132 patients with untreated metastatic or unresectable, locally recurrent HNSCC regardless of PD-L1 status will be randomized in a 1:1 ratio to receive either magrolimab + pembrolizumab + platinum + 5-FU (Arm A) or pembrolizumab + platinum + 5-FU (Arm B). The primary efficacy assessment will be PFS by as determined by investigator assessment, with the primary analysis to occur after 93 events. Stratification factors for randomization include the following:

- PD-L1 expression (CPS ≥ 1 versus CPS < 1)

- p16 status (positive versus negative)

Once the Phase 2 Cohort 1 enrolls 20 patients in each arm, a third arm will open: magrolimab + zimberelimab + platinum + 5-FU (Arm C; n = 46). Randomization will continue 1:1:1 across all 3 arms, with the same stratification factors.

3.1.2.2. Phase 2 Cohort 2

Dose finding for magrolimab + pembrolizumab alone (without chemotherapy) may be performed by the sponsor, as needed. An optional Phase 2 Cohort 2 will open for enrollment once the RP2D for magrolimab + pembrolizumab is determined. Approximately 25 patients with untreated

metastatic or unresectable, locally recurrent HNSCC with a PD-L1 CPS ≥ 1 will be enrolled to receive magrolimab + pembrolizumab. The primary efficacy assessment will be investigator-assessed ORR.

3.1.2.3. Phase 2 Cohort 3

Once the SRT reviews Safety Run-in 2 and the sponsor determines the RP2D for magrolimab + docetaxel, the Phase 2 Cohort 3 will open for enrollment. Approximately 40 patients with locally advanced/mHNSCC regardless of PD-L1 status who were previously treated with at least 1 and no more than 2 lines of prior systemic therapy will be enrolled to receive magrolimab + docetaxel. The primary efficacy assessment will be investigator-assessed ORR.

3.1.3. Diagnostic Tissue Testing

Tumor expression of PD-L1 will be evaluated prospectively using an assay approved by the FDA for detection of PD-L1 in HNSCC tissues.

Testing for p16 HPV positivity will be performed by immunohistochemistry analysis using the CINtec® Histology (p16) assay (Ventana Medical Systems, Inc., Tucson, AZ). A central laboratory may be used if testing as specified is not available locally. Oral cavity, hypopharynx, and larynx cancers are not required to undergo HPV testing by immunohistochemistry, as by convention they are assumed to be HPV negative.

3.2. Study Treatments

3.2.1. Safety Run-in 1, Pre-expansion Safety Run-in for Magrolimab + Pembrolizumab (if Applicable), and Phase 2 Cohorts 1 and 2

Study treatments for Safety Run-in 1 and Phase 2 Cohort 1 are summarized in Table 2 and Table 3, respectively. For platinum usage, cisplatin or carboplatin can be used per investigator choice. The schedules of assessments are provided in Appendix 2.

Table 2. Safety Run-in 1: Dose De-escalation

Dose Level	Drug/Dose/Route	Dose Schedule (Day per 21-Day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
Starting dose	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 30 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 60 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1
	5-FU 1000 mg/m^2/day continuous IV	Days 1-4	Days 1-4	Days 1-4 Cycles 3-6
	Cisplatin 100 mg/m^2 IV (1 h) or Carboplatin AUC 5 IV (1 h)	Day 1	Day 1	Day 1 Cycles 3-6
Level minus 1	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 20 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 45 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1
	5-FU 1000 mg/m^2/day continuous IV	Days 1-4	Days 1-4	Days 1-4 Cycles 3-6
	Cisplatin 100 mg/m^2 IV (1 h) or Carboplatin AUC 5 IV (1 h)	Day 1	Day 1	Day 1 Cycles 3-6
Level minus 2	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 15 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 30 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1
	5-FU 1000 mg/m^2/day continuous IV	Days 1-4	Days 1-4	Days 1-4 Cycles 3-6
	Cisplatin 100 mg/m^2 IV (1 h) or Carboplatin AUC 5 IV (1 h)	Day 1	Day 1	Day 1 Cycles 3-6

5-FU = 5-fluorouracil; IV = intravenous

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

Treatment Group	Drug/Dose/Route	Dose Schedule (Day per 21-Day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
Magrolimab + pembrolizumab + platinum + 5-FU	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab[a] IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab[a] IV (2 h ± 30 min)	—	—	Day 1
	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1
	5-FU 1000 mg/m^2/day continuous IV	Days 1-4	Days 1-4	Days 1-4 Cycles 3-6
	Cisplatin 100 mg/m^2 IV (1 h) or Carboplatin AUC 5 IV (1 h)	Day 1	Day 1	Day 1 Cycles 3-6
Pembrolizumab + platinum + 5-FU	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1
	5-FU 1000 mg/m^2/day continuous IV	Days 1-4	Days 1-4	Days 1-4 Cycles 3-6
	Cisplatin 100 mg/m^2 IV (1 h) or Carboplatin AUC 5 IV (1 h)	Day 1	Day 1	Day 1 Cycles 3-6
Magrolimab + Zimberelimab + platinum + 5-FU	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab[a] IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab[a] IV (2 h ± 30 min)	—	—	Day 1
	Zimberelimab 360 mg IV (60 min ± 15 min)	Day 1	Day 1	Day 1
	5-FU 1000 mg/m^2/day continuous IV	Days 1-4	Days 1-4	Days 1-4 Cycles 3-6
	Cisplatin 100 mg/m^2 IV (1 h) or Carboplatin AUC 5 IV (1 h)	Day 1	Day 1	Day 1 Cycles 3-6

5-FU = 5-fluorouracil; IV = intravenous; RP2D = recommended Phase 2 dose
a RP2D as determined in Safety Run-in 1, as described in Table 2.

If the sponsor determines that additional dose finding for magrolimab + pembrolizumab (alone without chemotherapy) is needed, all patients in the pre-expansion safety run-in evaluation will receive magrolimab + pembrolizumab. Study treatments for the pre-expansion safety run-in for magrolimab + pembrolizumab and Phase 2 Cohort 2 are summarized in Table 4 and Table 5, respectively. The schedules of assessments are provided in Appendix 2.

Table 4. Pre-expansion Safety Run-in for Magrolimab + Pembrolizumab: Dose De-escalation

Dose Level	Drug/Dose/Route	Dose Schedule (Day per 21-Day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
Starting dose	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 30 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 60 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1
Level minus 1	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 20 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 45 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1
Level minus 2	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 15 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 30 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1

IV = intravenous

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

Treatment Group	Drug/Dose/Route	Dose Schedule (Day per 21-Day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
Magrolimab + pembrolizumab	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab[a] IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab[a] IV (2 h ± 30 min)	—	—	Day 1
	Pembrolizumab 200 mg IV (30 min ± 10 min)	Day 1	Day 1	Day 1

IV = intravenous; RP2D = recommended Phase 2 dose
a RP2D as determined in the pre-expansion safety run-in for magrolimab + pembrolizumab (if applicable), as described in Table 4.

3.2.2. Safety Run-in 2 and Phase 2 Cohort 3

Study treatments for Safety Run-in 2 and Phase 2 Cohort 3 are summarized in Table 6 and Table 7, respectively. The schedules of assessments are provided in Appendix 2.

Table 6. Safety Run-in 2: Dose De-escalation

Dose Level	Drug/Dose/Route	Dose Schedule (Day per 21-Day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
Starting dose	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 30 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 60 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Docetaxel 75 mg/m^2 IV (1 h ± 5 min)	Day 1	Day 1	Day 1
Level minus 1	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 20 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 45 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Docetaxel 75 mg/m^2 IV (1 h ± 5 min)	Day 1	Day 1	Day 1
Level minus 2	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab 15 mg/kg IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab 30 mg/kg IV (2 h ± 30 min)	—	—	Day 1
	Docetaxel 75 mg/m^2 IV (1 h ± 5 min)	Day 1	Day 1	Day 1

IV = intravenous

Table 7. Phase 2 Cohort 3: Dose Level and Schedule

Treatment Group	Drug/Dose/Route	Dose Schedule (Day per 21-Day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
Magrolimab + docetaxel	Magrolimab 1 mg/kg IV (3 h ± 30 min)	Day 1	—	—
	Magrolimab[a] IV (2 h ± 30 min)	Days 8 and 15	Days 1, 8, and 15	—
	Magrolimab[a] IV (2 h ± 30 min)	—	—	Day 1
	Docetaxel 75 mg/m^2 IV (1 h ± 5 min)	Day 1	Day 1	Day 1

IV = intravenous; RP2D = recommended Phase 2 dose
a RP2D as determined in Safety Run-in 2, as described in Table 6.

3.3. Duration of Treatment

Cycle length is 21 days for all cohorts. Magrolimab and docetaxel will be continued until loss of clinical benefit, unacceptable toxicity, or death. Pembrolizumab and zimberelimab therapies will be administered for up to 24 months or until loss of clinical benefit or unacceptable toxicity, whichever occurs first. Platinum + 5-FU will be administered for up to 6 cycles or until loss of clinical benefit or unacceptable toxicity, whichever occurs first.

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 immune-related Response Evaluation Criteria in Solid Tumors (irRECIST). If any drug from the combination regimen is discontinued for reasons other than disease progression, the remaining drug(s) in the combination regimen may be continued. Patients are

not required to discontinue study drug for disease progression per RECIST criteria, given the observation that delayed clinical benefit can occur with immune therapies beyond initial disease progression. Treatment with study drug may continue past the initial determination of disease progression according to irRECIST if the following criteria are met:

- No new symptoms or worsening of previous symptoms
- Tolerance of magrolimab + pembrolizumab + platinum + 5-FU, magrolimab + zimberelimab + platinum + 5-FU, magrolimab + pembrolizumab, or magrolimab + 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 (eg, central nervous metastases).

The decision to continue treatment should be approved by the sponsor.

3.4. Discontinuation Criteria

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

- Disease progression by irRECIST (treatment beyond disease progression by irRECIST 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 treatment beyond irRECIST disease progression in accordance with criteria in Section 3.3. All patients must be followed through completion of all study treatment.

3.5. Discontinuation From Study Criteria/End of Study

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

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

All patients will be followed for survival until death, withdraw from consent, lost to follow-up, or 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, subsequent therapy, and response to subsequent therapy, survival, and AEs as specified in Appendix Table 2. See Appendix 12 for poststudy care considerations in France.

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 indication studied, as well as the efficacy and mechanism of action 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, but will not be limited to, the following:

- Blood sample for RO (at select sites)
- Circulating tumor DNA sample to monitor treatment response

- Peripheral blood mononuclear cell (PBMC) to assess immune cell phenotypes
- 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 assays
- T-cell receptor sequencing sample to assess immune repertoire changes
- Stool samples to assess microbiome
- Mandatory baseline tumor tissue and on-treatment biopsy 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 2).

Blood and tumor samples will also be used for genomic research. In addition, a whole blood genomic 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 mechanism of action 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.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4. PATIENT POPULATION

4.1. Number of Patients and Patient Selection

Approximately 230 and up to 297 patients may be enrolled in the study, with at least 12 and up to 54 patients in total in Safety Run-ins 1 and 2, and optional Pre-expansion Safety Run-in for Cohort 2; approximately 178 patients in Phase 2 Cohort 1; approximately 25 patients in optional Phase 2 Cohort 2; and approximately 40 patients in Phase 2 Cohort 3.

4.1.1. Patient Replacement

Patients may be replaced in the safety run-in evaluations if not evaluable for DLT assessment, as described in Section 3.1.1.

4.2. Inclusion Criteria

All Patients

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) ECOG performance status of ≤ 1.
5) Laboratory measurements, blood counts:
    a) Hemoglobin must be ≥ 9 g/dL prior to initial dose of study treatment. Red blood cell transfusions are allowed to meet hemoglobin eligibility within limits set per Exclusion Criterion #6 (and per Section 7.8.1.2).
    b) Absolute neutrophil count (ANC) ≥ 1.5×10^9/L.
    c) Platelets ≥ 100×10^9/L.
6) Laboratory measurements, renal function:
    a) Serum creatinine ≤ 1.5 × ULN or if elevated, a calculated glomerular filtration rate > 40 mL/min/1.73 m^2.
7) Laboratory measurements, hepatic function:
    a) AST and ALT ≤ 2.5 × ULN or ≤ 5 × ULN in patients with liver metastases.
    b) Total bilirubin ≤ 1.5 × ULN or ≤ 3.0 × ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or genetic equivalent.

8) Laboratory measurements, coagulation function:

   a) International normalized ratio or prothrombin time (PT) ≤ 1.5 × ULN unless patient is receiving anticoagulation therapy, as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use for anticoagulants.

   b) Activated partial thromboplastin time or PTT ≤ 1.5 × ULN unless patient is receiving anticoagulation therapy, as long as PT or PTT is within therapeutic range of intended use for anticoagulants.

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

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

11) Measurable disease according to RECIST, Version 1.1.

12) Note: Inclusion Criterion #12 was removed in Protocol Amendment 3 and relocated to Inclusion Criterion #13d.

Safety Run-in 1, Pre-expansion Safety Run-in for Magrolimab + Pembrolizumab (if Applicable), and Phase 2 Cohorts 1 and 2

In addition to meeting the inclusion criteria for all patients, patients who are enrolled into Safety Run-in 1, the pre-expansion safety run-in for magrolimab + pembrolizumab (if applicable), and Phase 2 Cohorts 1 and 2 must fulfill the following cohort-specific inclusion criterion:

13) Histologically or cytologically confirmed metastatic or locally recurrent HNSCC that is considered incurable by local therapies

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

   b) Eligible primary tumor locations include oropharynx, oral cavity, hypopharynx, and larynx.

   c) Patients may not have a primary tumor site of nasopharynx (any histology).

   d) Patients must be willing to provide baseline tumor tissue from a core or excisional biopsy (fine needle aspirate is not adequate). A newly obtained biopsy (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 be requested to consent to a mandatory on-treatment tumor biopsy, unless not feasible as determined by the investigator and discussed with the sponsor.

Safety Run-in 1 and Phase 2 Cohort 1

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

14) Patients with HNSCC per Inclusion Criterion #13 regardless of PD-L1 status.

Pre-expansion Safety Run-in for Magrolimab + Pembrolizumab (if Applicable) and Phase 2 Cohort 2

In addition to meeting the inclusion criteria for all patients, patients who are enrolled into the pre-expansion safety run-in for magrolimab + pembrolizumab (if applicable) and Phase 2 Cohort 2 must fulfill the following cohort-specific inclusion criterion:

15) Patients with HNSCC per Inclusion Criterion #13 with a PD-L1 CPS ≥ 1.

Safety Run-in 2 and Phase 2 Cohort 3

In addition to meeting the inclusion criteria for all patients, patients who are enrolled into Safety Run-in 2 and Phase 2 Cohort 3 must fulfill the following cohort-specific inclusion criterion:

16) Patients with histologically or cytologically confirmed locally advanced/mHNSCC regardless of PD-L1 status with at least 1 and no more than 2 lines of prior systemic anticancer therapy in the locally advanced/metastatic setting

    a) Eligible primary tumor locations include oropharynx, oral cavity, hypopharynx, and larynx.

    b) Patients may not have a primary tumor site of nasopharynx (any histology).

    c) Prior systemic anticancer therapy for locally advanced/mHNSCC should consist of at least 1 line of platinum-based chemotherapy, with or without a PD-1 inhibitor. For patients with CPS ≥ 1 HNSCC, prior systemic anticancer therapy for locally advanced/mHNSCC should have included at least one line of PD-1 inhibitor-based therapy unless medically contraindicated.

4.3. Exclusion Criteria

All Patients

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

1) Prior radiation therapy (or other nonsystemic therapy) within 2 weeks prior to enrollment. Patients who are candidates for curative radiation therapy are not eligible.

2) Patient has not fully recovered (ie, ≤ Grade 1 at baseline) from AEs due to a previously administered treatment.

    a) Note: Patients with ≤ Grade 2 neuropathy, ≤ Grade 2 alopecia, or laboratory values in inclusion criteria 5 through 8 are exceptions to this criterion and may qualify for the study.

    b) Note: If a patient received major surgery, he or she must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3) Positive serum pregnancy test (Appendix 5).

4) Breastfeeding female.

5) Active CNS disease (patients with asymptomatic and stable, treated CNS lesions who have been off corticosteroids, radiation, or other CNS-directed therapy for at least 4 weeks are not considered active).

6) 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 criterion.

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

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

    a) For Phase 2 Cohort 1, complete absence of dihydropyrimidine dehydrogenase (DPD) activity. If DPD status is not known, testing for DPD status should be done during the screening period where such testing is standard of care.

9) Prior treatment with CD47 or SIRPα-targeting agents.

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

11) Life expectancy of less than 3 months and/or rapidly progressing disease (eg, tumor bleeding, uncontrolled tumor pain) in the opinion of the treating investigator.

12) Diagnosis of immunodeficiency or receipt of systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study therapy. Corticosteroid use as a premedication for allergic reactions or for prophylactic management of AEs related to the chemotherapies specified in the protocol is allowed. The use of physiologic doses of corticosteroids may be approved with approval by the sponsor.

13) Active autoimmune disease that has required systemic treatment in the past 2 years (ie, use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.

14) Prior allogeneic tissue/solid organ transplant.

15) History of (noninfectious) pneumonitis that required steroids or current pneumonitis.

16) Active, uncontrolled infection or infection requiring systemic therapy within ≤ 7 days of study entry.

17) Live vaccine within 30 days of start of study treatment.

18) Current participation in another interventional clinical study.

19) Known inherited or acquired bleeding disorders.

20) 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.

21) 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 5 years.

22) In patients with known history of HIV, presence of detectable viral load. HIV testing will be performed at screening only if required by local guidelines or institutional standards.

23) Known positivity for hepatitis B or C infection. Patients not currently on antiviral therapy and who have an undetectable viral load in the prior 3 months may be eligible for the study. Hepatitis B or C testing is not required. Patients with serologic evidence of prior vaccination to hepatitis B virus (ie, hepatitis B surface antigen negative and antibody against hepatitis B surface antigen positive) may participate.

<u>Safety Run-in 1, Pre-expansion Safety Run-in for Magrolimab + Pembrolizumab (if Applicable), and Phase 2 Cohorts 1 and 2</u>

Patients who meet *any* of the following exclusion criteria are not eligible to be enrolled into Safety Run-in 1, the pre-expansion safety run-in for magrolimab + pembrolizumab (if applicable), or Phase 2 Cohorts 1 and 2:

24) Progressive disease within 6 months of completion of curatively intended treatment for locoregionally advanced HNSCC.

25) Prior treatment with any of the following:

    a) Anti–PD-1 or anti–PD-L1 checkpoint inhibitors.

    b) Anti–cytotoxic T-lymphocyte–associated protein 4 checkpoint inhibitors.

Safety Run-in 2 and Phase 2 Cohort 3

Patients who meet *any* of the following exclusion criteria are not eligible to be enrolled into Safety Run-in 2 or Phase 2 Cohort 3:

26) Progressive disease within 6 months of completion of curatively intended treatment for locally advanced/mHNSCC.

27) Prior treatment with a taxane.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding, and Treatment Codes Access

5.1.1. Randomization

Patients in Phase 2 Cohort 1 of the study who meet eligibility criteria will be randomized in a 1:1 ratio to receive either magrolimab + pembrolizumab + platinum + 5-FU (Arm A) or pembrolizumab + platinum + 5-FU (Arm B) using an IRT. The first dose on Day 1 must be administered within 3 days of randomization. Once the Phase 2 Cohort 1 enrolls 20 patients in each arm, a third arm will open: magrolimab + zimberelimab + platinum + 5-FU (Arm C). Randomization will continue 1:1:1 across all 3 arms.

Randomization will be stratified by the following: 1) PD-L1 expression (CPS $\geq$ 1 versus CPS < 1) and 2) p16 status (positive versus negative).

5.1.2. Blinding

Blinding of treatment assignments or data will not be performed in this open-label 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) Guidelines 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-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 Pembrolizumab

5.3.1. Formulation

Pembrolizumab is commercially sourced. Information regarding the formulation can be found in the current country-specific prescribing information.

5.3.2. Packaging and Labeling

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

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

5.4. Description and Handling of Zimberelimab

5.4.1. Formulation

Zimberelimab Injection, 30 mg/mL drug product will be supplied as a sterile, preservative-free, clear, colorless, and slightly opalescent solution for IV administration. The drug product is composed of 30 mg/mL zimberelimab in 20 mM histidine/histidine-HCl, 150 mM sucrose, 45 mM NaCl, 0.02% (weight/volume) polysorbate 80 at pH 5.5.

5.4.2. Packaging and Labeling

Zimberelimab Injection, 30 mg/mL drug product is filled in single-use, 8R, Type I clear glass vials with coated elastomeric stoppers and capped with polypropylene flip-off caps with aluminum overseals.

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

5.4.3. Storage and Handling

Zimberelimab should be stored at 2 °C to 8 °C (36 °F-46 °F). Zimberelimab should not be frozen and should be protected from light during storage. 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.

5.5. Description and Handling of 5-Fluorouracil

5.5.1. Formulation

5-Fluorouracil is commercially sourced. Information regarding the formulation can be found in the current country-specific prescribing information.

5.5.2. Packaging and Labeling

Commercial product of 5-FU will be used for this study. Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guidelines to Good Manufacturing Practice, 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.

5.5.3. Storage and Handling

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

5.6. Description and Handling of Cisplatin

5.6.1. Formulation

Cisplatin is commercially sourced. Information regarding the formulation can be found in the current country-specific prescribing information.

5.6.2. Packaging and Labeling

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

5.6.3. Storage and Handling

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

5.7. Description and Handling of Carboplatin

5.7.1. Formulation

Carboplatin is commercially sourced. Information regarding the formulation can be found in the current country-specific prescribing information.

5.7.2. Packaging and Labeling

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

5.7.3. Storage and Handling

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

5.8. Description and Handling of Docetaxel

5.8.1. Formulation

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

5.8.2. 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 Guidelines 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.

5.8.3. Storage and Handling

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

5.9. Dosage and Administration of Magrolimab

The magrolimab dosing regimen for each cohort is presented in Table 2 to Table 7.

Magrolimab should be administered as outlined in the Pharmacy Manual for the study. The dose of magrolimab will be calculated based on actual weight at 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 of the first magrolimab (priming) infusion will be 3 hours (± 30 minutes). For subsequent doses, the magrolimab (maintenance) infusion will be 2 hours (± 30 minutes). The reduced infusion time to 2 hours is utilized based on prior data demonstrating majority CD47 RO on peripheral blood cells, thus mitigating anticipated RBC toxicities from magrolimab.

Magrolimab doses will be given weekly during Cycles 1 and 2. Magrolimab will then be administered every 3 weeks during Cycle 3 and beyond. **Magrolimab doses are not to be given on consecutive days**.

When magrolimab is given in combination with pembrolizumab + platinum + 5-FU chemotherapy, zimberelimab + platinum + 5-FU, pembrolizumab, or docetaxel, magrolimab will be infused first. All patients should be monitored for 1 hour after infusion for priming, repriming, and maintenance doses during Cycle 1. Postinfusion monitoring should begin after the infusion is complete but prior to administering any other study drug. Postinfusion monitoring is not required for doses after Cycle 1 Day 15. Patients who experience any treatment-emergent AEs during the observation period should be further monitored, as clinically appropriate. Refer to Section 7.8.1.2 for postinfusion hemoglobin and hematocrit 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 provided in Section 3.4).

Treatment Delay and Repriming for Magrolimab

Given the large CD47 antigen sink on normal cells, patients who have a prolonged dose delay of magrolimab are required to be reprimed with magrolimab dosing to resaturate the CD47 antigen sink. Guidelines for repriming for magrolimab after a dose delay are provided in Section 5.9.1.

5.9.1. Dose Modifications and Delays for Magrolimab

In most circumstances, the dose of magrolimab should not be reduced. 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.

Magrolimab should be withheld for any treatment-related Grade 4 AE, Grade 3 hemolytic anemia that is medically significant (requiring hospitalization or prolongation of existing hospitalization, disabling, or limiting self-care activities of daily life) or unmanageable any-grade toxicity. Magrolimab may be reintroduced once the severity is Grade $\leq$ 2 or baseline. Depending on the duration of the dose hold, repriming may be required as outlined in Table 8. See also Section 7.8.1.6 regarding magrolimab dose delays for severe neutropenia and Section 7.8.1.7 regarding magrolimab dose delays for serious infections.

When combination drug treatment is delayed due to toxicities, magrolimab should be continued 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 onward), 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 combination drug administration.

The repriming guidelines shown in Table 8 should be followed for patients with dose delays. During repriming, efficacy, biomarker, PK, and immunogenicity assessments should follow the schedule of the assigned cycle number. Magrolimab dosing and safety assessments should follow Cycle 1 (refer to Table 2 to Table 7, as appropriate) and then subsequently switch back to the

assigned cycle schedule (Appendix Table 1). 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 Cycle 3.

Criteria for permanent discontinuation of magrolimab include the following:

- Grade 4 IRR, or recurrent Grade 3 IRR despite premedication, as per Section 7.8.1.3
- 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 8. 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
	Every 3 weeks	4 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 9.

Table 9. 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

Planned Surgical Procedure	Magrolimab Dose Guidance
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

5.9.2. 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.

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 a comparable regimen. Premedication decisions for subsequent infusions should be based on the treating physician's clinical judgment and the presence/severity of prior IRRs (guidance is provided in Section 7.8.1.3 Management of Infusion-Related Reactions).

5.10. Dosage and Administration of Pembrolizumab

The pembrolizumab dosing regimen for each cohort is presented in Table 2 to Table 5.

Pembrolizumab will be administered at a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to ensure infusion timing is as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between −10 minutes and +10 minutes is permitted.

5.10.1. Dose Modifications for Pembrolizumab

Temporary suspension or permanent discontinuation of pembrolizumab may be required in the event of treatment-related toxicity. Dose reductions are not permitted. See Section 7.8.2 for recommendations for management of toxicities.

5.11. Dosage and Administration of Zimberelimab

The zimberelimab dosing regimen is presented in Table 3.

Zimberelimab will be administered at a dose of 360 mg IV, using a 60 (± 15 minutes)-minute infusion. All patients will be monitored for 30 to 60 minutes after the end of each infusion. Postinfusion monitoring should begin after the zimberelimab infusion is complete and prior to administering subsequent study drugs.

5.11.1. Dose Modifications for Zimberelimab

Temporary suspension or permanent discontinuation of zimberelimab may be required in the event of treatment-related toxicity. Dose reductions are not permitted. See Section 7.8.3 for recommendations for management of toxicities.

5.12. Dosage and Administration of 5-Fluorouracil

The 5-FU dosing regimen for Safety Run-in 1 and Phase 2 Cohort 1 is presented in Table 2 and Table 3, respectively.

5-Fluorouracil will be administered as a continuous infusion from Days 1 to 4 of each treatment cycle. On Day 1 of each treatment cycle, the 5-FU infusion should be started after completion of all procedures and assessments according to the schedule of assessments (Appendix Table 1).

5.12.1. Dose Modifications for 5-Fluorouracil

Dose modification guidelines for 5-FU for febrile neutropenia or documented infection and drug-related AEs are described in Table 10, Table 11, and Table 12. If 5-FU is discontinued for reasons other than disease progression, the remaining drug(s) in the combination regimen may be continued.

Table 10. 5-Fluorouracil Dose Modification Levels

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

5-FU = 5-fluorouracil

Table 11. 5-Fluorouracil Dose Modification Guidelines for Febrile Neutropenia or Documented Infection

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

5-FU = 5-fluorouracil

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

Table 12. 5-Fluorouracil Dose Modification Guidelines for Drug-Related Adverse Events

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

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

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

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

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

c Restarting 5-FU should occur on Day 1 of the next cycle after criteria for restarting has been met.

5.13. Dosage and Administration of Platinum (Cisplatin or Carboplatin)

Cisplatin or carboplatin can be administered in Safety Run-in 1 and Phase 2 Cohort 1 per investigator choice. The platinum dosing regimen for Safety Run-in 1 and Phase 2 Cohort 1 is presented in Table 2 and Table 3, respectively.

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

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

5.13.1. Dose Modifications for Platinum (Cisplatin or Carboplatin)

Investigators may switch patients from cisplatin to carboplatin during the study if toxicities occur. If the cisplatin dose was modified prior to switching, the patient may start at a carboplatin dose of AUC 5 and will be eligible to receive additional 2 dose modifications of carboplatin. Platinum dose modification guidelines for febrile neutropenia or documented infection and drug-related AEs are described in Table 13, Table 14, and Table 15. If platinum is discontinued for reasons other than disease progression, the remaining drug(s) in the combination regimen may be continued.

Table 13. Platinum Dose Modification Levels

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

Table 14. Platinum Dose Modification Guidelines for Febrile Neutropenia or Documented Infection

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

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

Table 15. Platinum Dose Modification Guidelines for Drug-Related Adverse Events

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

Category	Toxicity	Hold Platinum Treatment for Grade	Timing for Restarting Platinum Treatment[c]	Dose for Restarting Platinum Treatment	Discontinue Platinum
Nonhematologic	Creatinine increased	2 to 4[a]	Toxicity resolves to Grade 0 or 1	For patients taking carboplatin, reduce by 1 dose level. For patients taking cisplatin, change cisplatin to carboplatin.	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded
	Ototoxicity or sensory neuropathy	2	Change cisplatin to carboplatin May continue treatment with carboplatin		
		3 or 4[a]	May switch cisplatin to carboplatin if resolves to ≤ Grade 2 within 12 weeks of last infusion If already using carboplatin, then discontinue		
	All other nonhematologic toxicities[b]	3 or 4[a]	Toxicity resolves to Grade 0 or 1	Reduce by 1 dose level	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded
	Laboratory AE[b]	4[a]	Toxicity resolves to ≤ Grade 2	Reduce by 1 dose level	Toxicity does not resolve within 12 weeks of last infusion or if > 2 dose level reductions exceeded

AE = adverse event; G-CSF = granulocyte colony-stimulating factor
a Permanent discontinuation should be considered for any severe or life-threatening event. Consult the sponsor before restarting treatment after a Grade 4 drug-related AE.
b Patients with an intolerable or persistent Grade 2 drug-related AE may hold dosing at the physician's discretion. Permanently discontinue platinum for persistent Grade 2 adverse reactions for which treatment has been held and that do not improve to Grade 0 or 1 within 12 weeks of the last dose. With investigator and sponsor agreement, patients with a laboratory AE still at Grade 2 after 12 weeks may continue in the study only if asymptomatic and the AE does not worsen.
c Restarting platinum should occur on Day 1 of the next cycle after criteria for restarting has been met.

5.14. Dosage and Administration of Docetaxel

The docetaxel dosing regimen for Safety Run-in 2 and Phase 2 Cohort 3 is presented in Table 6 and Table 7, respectively. Docetaxel will be administered at a dose of 75 mg/m^2 using a 60-minute (± 5 minutes) IV infusion (or an infusion duration according to local practice).

5.14.1. 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 and are in accordance with the docetaxel prescribing information.

5.14.1.1. Neutropenia

Docetaxel causes neutropenia; guidance on dose reductions is shown in Table 16. Patients should have an ANC ≥ 1500 cells/μL before initiating the next cycle of docetaxel therapy. Myeloid growth factor support is allowed per institutional guidelines.

Table 16. Docetaxel Dose Modification Guidelines for Neutropenia

Hematologic Toxicity	Occurrence	Docetaxel Dose (mg/m^2) per Cycle
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

5.14.1.2. Hepatic Toxicity

Docetaxel should be withheld for Grade 3 or 4 hepatic toxicity deemed related to docetaxel as specified in Table 17. In addition, the investigator should make every effort to exclude malignant disease progression as a cause of liver enzyme derangement, which would not be considered a toxicity for docetaxel.

Table 17. Docetaxel Dose Modification Guidelines for Hepatic Toxicity

Hepatic Toxicity	Occurrence	Docetaxel Dose Modification
AST or ALT > 1.5 × ULN (or baseline if higher) and alkaline phosphatase > 2.5 × ULN or Bilirubin > 1.25 × ULN	First	Interrupt treatment until AST/ALT ≤ 1.5 × ULN and alkaline phosphatase ≤ 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 ≤ 1.5 × ULN and alkaline phosphatase ≤ 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	Any	Discontinue treatment
Bilirubin > 5 × ULN	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

5.14.1.3. Peripheral Neuropathy

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

5.14.1.4. Other Toxicities

Docetaxel dose modifications for other Grade 3 or 4 hematologic or nonhematologic toxicities deemed related to docetaxel are shown in Table 18. Docetaxel should be delayed until improvement of the Grade 3 or 4 toxicity to at least Grade 2 or baseline.

Table 18. Docetaxel Dose Modification Guidelines for Other Grade 3 or 4 Toxicities

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

a Grade 3 or 4 nonhematologic or hematologic toxicities apply to those not described in the above dose modification sections.

5.14.2. 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 once per day (eg, 8 mg twice daily) for 3 days starting 1 day prior to docetaxel administration. 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.

5.15. Prior and Concomitant Medications

5.15.1. 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 (see Section 7.8.1.6), hormonal therapy, luteinizing hormone-releasing hormone agonists for prostate cancer, hormonal maintenance therapy for breast cancers, and treatment with bisphosphonates/receptor activator of nuclear factor kappa-B ligand inhibitors are permitted.

For patients receiving zimberelimab, immunosuppressive medications, including chronic systemic corticosteroids at supraphysiologic doses (physiologic doses being equivalent to a dose of ≤ 10 mg oral prednisone) 14 days before the first dose (except for patients who require hormone replacement therapy such as hydrocortisone) is not permitted nor while receiving study therapy. A temporary course of corticosteroids (ie, contrast allergy, chronic obstructive pulmonary disease) may be permitted, depending on the duration and dose, after discussion and agreement with the medical monitor. For all other patients, corticosteroid use is permitted for symptomatic treatment, premedication, pseudoprogression, and/or specific patient conditions.

Inhaled and topical corticosteroid use is permitted. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor. Chronic high-dose steroid use is not recommended.

Red blood cell and platelet transfusion are permitted during the study as clinically indicated and should be recorded in the electronic case report form (eCRF) dedicated to on study transfusions.

All concomitant medications, including 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 (or 90-day safety follow-up for zimberelimab) should be recorded in the eCRF. The drug name, indication, route, dose, and dates of concomitant medications will be captured in the eCRF.

5.15.2. Prohibited Concomitant Medications

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

Live vaccines within 30 days before the first dose of study treatment and while patients are on study treatment are not permitted. Radiation therapy is not permitted unless it is localized radiation therapy to a solitary lesion and after discussion with the sponsor.

5.16. Timing of Dose Administration

For Safety Run-in 1 and Phase 2 Cohort 1, magrolimab should be administered prior to pembrolizumab or zimberelimab, followed by platinum and 5-FU. For the pre-expansion safety run-in for magrolimab + pembrolizumab (if applicable) and Phase 2 Cohort 2, magrolimab should be administered prior to pembrolizumab. Magrolimab and pembrolizumab or zimberelimab should be administered on the same day unless administrative reasons do not allow, or to accommodate the patient's schedule, in which case pembrolizumab or zimberelimab may be administered on Day 2 of each cycle at the investigator's discretion. For Safety Run-in 2 and Phase 2 Cohort 3, magrolimab should be administered prior to docetaxel. Magrolimab should be administered 1 hour prior to the next IV drug delivery. Magrolimab postinfusion monitoring should occur as described in Section 5.9.

To accommodate the patient's schedule, platinum chemotherapy may be administered on Day 2 of each cycle at the investigator's discretion.

5.17. 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 (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

5.17.1. Investigational Medicinal Product Return or Disposal

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

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

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

6. STUDY PROCEDURES

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

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

6.1. Patient Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment into 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 in Safety Run-in 1 will receive magrolimab + pembrolizumab + platinum + 5-FU. Treatment assignment for patients in Phase 2 Cohort 1 will be randomized using IRT. Patients will be assigned to receive magrolimab + pembrolizumab + platinum + 5-FU (Arm A) or pembrolizumab + platinum + 5-FU (Arm B) in a 1:1 ratio. After 40 patients have been enrolled (20 in each arm), Arm C (magrolimab + zimberelimab + platinum + 5-FU) will open and patients will be randomized in a 1:1:1 ratio.

All patients in the pre-expansion safety run-in for magrolimab + pembrolizumab (if applicable) and Phase 2 Cohort 2 will receive magrolimab + pembrolizumab.

All patients in Safety Run-in 2 and Phase 2 Cohort 3 will receive magrolimab + docetaxel. Once the SRT reviews the Safety Run-in 2 and the sponsor determines the RP2D for magrolimab + docetaxel, Phase 2 Cohort 3 will open for enrollment.

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. Standard-of-care procedures performed before obtaining informed consent may be used for screening (with the exception of the following tests shown in Table 19, which must be drawn after obtaining informed consent and conducted by the central laboratory: chemistry, hematology, coagulation, urinalysis, thyroid function, and serum pregnancy samples). Refer to Section 6.6 regarding use of tumor imaging obtained prior to enrollment. The following will be performed and documented at screening per Appendix Table 1:

- 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; thyroid panel; blood phenotyping, type, and screen; and direct antiglobulin test (DAT) (Section 6.4.2). Blood for biomarker samples will also be collected (ie, serum and plasma, and circulating tumor DNA)
- Tumor biopsy
- Tumor imaging
- ECOG
- Perform 12-lead electrocardiogram (ECG) (single)
- Record all serious adverse events (SAEs) 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 only SAEs related to protocol-mandated procedures on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be considered medical history. See Section 7, Adverse Events and Toxicity Management, for additional details.

6.3. Randomization

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

6.4. Treatment Assessments

6.4.1. Pregnancy Test

Pregnancy tests are required only for female patients of childbearing potential. Note that a woman is considered to be of childbearing potential following the initiation of puberty (Tanner Stage 2) until becoming postmenopausal, unless permanently sterile or with medically documented ovarian failure. Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female patient of any age. Women are considered to be in a postmenopausal state when they are ≥ 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. A negative serum pregnancy test is required at screening, and a negative urine pregnancy test is required prior to study treatment administration on Cycle 1 Day 1. The Cycle 1 Day 1 urine pregnancy test does not need to be conducted if the screening pregnancy test was performed within the 3 days before study treatment administration. Urine pregnancy tests will also be required at Cycle 2 Day 1 and every cycle thereafter and continue monthly up to 6 months after the end of treatment per the duration of required contraception as discussed in Appendix 5.

6.4.2. Type and Screen and Direct Antiglobulin Test

Due to the risk of developing anemia, and because magrolimab may make phenotyping difficult due to expected coating of the RBC membrane, ABO (any of the 4 blood groups A, B, AB, and O comprising the ABO system)/rhesus (Rh) factor type, antibody screen, blood phenotyping or genotyping, and DAT need to be performed at screening before exposure to magrolimab. Red blood cell genotyping (instead of an extended RBC phenotyping) must be performed if a patient received any RBC or whole blood transfusion within the previous 3 months (unless the laboratory has availability for special techniques for performing phenotyping for patients with a recent transfusion). Extended RBC genotyping instead of extended RBC phenotyping is acceptable for any patient. Red blood cell phenotyping/genotyping, ABO type, and DAT need not be repeated if results dated before screening are available. Antibody screen need not be repeated if results dated before screening are available, unless the patient was transfused since that time. Results must be available before the first dose of magrolimab.

6.4.3. Vital Signs

Vital signs will 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 dosing of study treatment at the visits specified in the schedule of assessments (Appendix Table 1).

6.4.4. Physical Examination

Complete physical examination will 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 9).

6.4.6. Electrocardiograms

A single ECG will be performed at screening.

Refer to Appendix 12 for zimberelimab monitoring requirements in Belgium.

6.4.7. Patient-Reported Outcomes

Three patient-reported outcomes (PROs) instruments will be administered in this study (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core- Questionnaire [EORTC QLQ-C30], European Organisation for Research and Treatment of Cancer Quality of Life - Head and Neck Module [EORTC QLQ-H&N35], and 5 level EuroQol-5 dimensions questionnaire [EQ-5D-5L]). The patient should complete these questionnaires before any other study procedures at required visits, with the exception of imaging, if applicable, and analytes to be assessed by the local and/or central laboratory or specialty laboratories during the study (Table 20 Appendix 2), which may be collected prior to the visit. Please refer to the schedules of assessments in Appendix 2 for timing of PRO assessments. If the PRO

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

6.4.7.1. EORTC QLQ-C30 and QLQ-H&N35

The EORTC QLQ-C30 is a reliable and valid measure of PROs and has been widely used among patients with cancer. The EORTC QLQ-C30 includes 30 separate questions (items) resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties) {Fayers 2001}. The recall period is 1 week (past week). It will take about 11 minutes to complete. The accompanying module for head and neck cancer, QLQ-H&N35, has an additional 35 questions.

6.4.7.2. EQ-5D-5L

The EQ-5D-5L is an instrument for use as a measure of health outcome {EuroQol Research Foundation 2017, Janssen 2013}. The EQ-5D-5L consists of 2 sections: the EQ-5D descriptive system and the EuroQol visual analogue scale (EQ-VAS). A sample is provided in Appendix 8.

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

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

6.4.8. Adverse Events

At each visit, all AEs observed by the investigator or reported by the patient that occur after the first dose of study treatment through 30 days after the last dose of study treatment (or 90 days after the last dose for zimberelimab) are to be reported using the applicable eCRF (Section 7.1.1). Full details on the definitions, assessment, and reporting instructions for AEs are provided in Section 7.

6.4.9. Concomitant Medications

All concomitant medications taken by the patient while on study are to be documented. Changes in baseline concomitant medication information is to be collected after informed consent through the study treatment period, and up until 30 days after treatment discontinuation (or 90 days after discontinuation of zimberelimab). Concomitant medication associated with procedure-related

AEs will be captured from the time of informed consent and onward. Information to be collected includes drug 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 schedule of assessments (Appendix Table 2).

6.5. Safety Assessments

Analytes to be assessed by the local and/or central laboratory or specialty laboratories at screening are presented in Table 19. Refer to Section 7.8.1.2 for hemoglobin and hematocrit testing requirements for the first 2 magrolimab doses predose and postdose monitoring.

Table 19. Screening Laboratory Analytes

Chemistry (Serum or Plasma)	Hematology	Urinalysis[a]	Other Laboratory Measurements[b]
Sodium Potassium Chloride Bicarbonate[c] Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or urea Creatinine Uric acid Total bilirubin Direct bilirubin Indirect bilirubin AST (SGOT) ALT (SGPT) Alkaline phosphatase	RBC Hemoglobin Hematocrit Platelets WBC total WBC differential ANC Eosinophils Basophils Lymphocytes Monocytes Reticulocytes **Coagulation** PT INR aPTT or PTT	Glucose Protein Urine pH Ketones Bilirubin Urine specific gravity	Pregnancy (serum) Blood phenotyping or genotyping[d] Type and screen (ABO/Rh)[d] DAT[d] T3 (total or free) FT4 TSH DPD[e] **Additional Samples** Tumor tissue (archival or from biopsy) p16 HPV[d] PD-L1[d]

ABO = any of the 4 blood groups A, B, AB, and O comprising the ABO system; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DAT = direct antiglobulin test; DPD = dihydropyrimidine dehydrogenase; FT4 = free thyroxine; HPV = human papillomavirus; INR = international normalized ratio; PD-L1 = programmed cell death ligand 1; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; Rh = rhesus; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; WBC = white blood cell

a Reflex microscopic testing based on other abnormalities.

b Refer to Appendix 12 for zimberelimab monitoring requirements in Belgium.

CCI [redacted]

d Test may be performed at a central laboratory or local laboratory, if available. For PD-L1 and p16 HPV, the local laboratory must use the protocol-specified assay.

e Where such testing is standard of care.

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

Analytes to be assessed by the local and/or central laboratory or specialty laboratories during the study are presented in Table 20.

Table 20. Study Laboratory Analytes (To Be Performed During the Study)

Chemistry (Serum or Plasma)	Hematology	Other Laboratory Measurements[a]
Sodium Potassium Chloride Bicarbonate[b] Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or urea Creatinine Uric acid Total bilirubin Direct bilirubin Indirect bilirubin AST (SGOT) ALT (SGPT) Alkaline phosphatase Haptoglobin LDH	RBC Hemoglobin Hematocrit Platelets WBC differential ANC Eosinophils Basophils Lymphocytes Monocytes Reticulocytes	Pregnancy (urine) Blood samples for correlative studies Pharmacokinetics Antidrug antibodies T3 (total or free) FT4 TSH **Additional Samples** Stool Tumor tissue from biopsy

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DAT = direct antiglobulin test; FT4 = free thyroxine; LDH = lactate dehydrogenase; RBC = red blood cell; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; WBC = white blood cell

a Refer to Appendix 12 for zimberelimab monitoring requirements in Belgium.

CCI [redacted]

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

6.6. Efficacy Assessments

Either computed tomography (CT), magnetic resonance imaging, or positron emission tomography-CT (that includes contrast-enhanced CT component) of the head, neck, chest, and abdomen will be performed at screening, every 6 weeks (2 cycles) until 36 weeks (Cycle 12) and then every 9 weeks (3 cycles) during the study (starting from Cycle 1 Day 1), and at the end-of-treatment visit if a response assessment has not been performed within the last 30 days or progressive disease has been documented. CCI [redacted] 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 6 or 9 weeks as clinically indicated to assess tumor progression.

For patients who stop study treatment in the absence of radiographic disease progression (eg, experienced unexpected toxicity), scans should continue to be collected approximately every 6 weeks (2 cycles) until 36 weeks (12 cycles) from Cycle 1 Day 1 and then every 9 weeks (3 cycles) until radiographic disease progression or initiation of systemic antitumor therapy other than the study treatment, whichever is earlier.

Patients will be assessed for response by the investigator or qualified designee using RECIST, Version 1.1 {Eisenhauer 2009} for the primary and secondary efficacy endpoints, irRECIST {Nishino 2013}will be used for treatment past initial determination of disease progression by RECIST 1.1.

6.7. Pharmacokinetic Assessments

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

Blood samples for PK assessment will be collected at predose at multiple time points from patients who received magrolimab according to the schedule of assessments in Appendix Table 1 CCI [redacted]

Zimberelimab serum concentration will be measured by a validated enzyme-linked immunosorbent assay immunoassay method.

Blood samples for PK assessment will be collected at predose and at the end of infusion on Cycle 1 Day 1 and Cycle 3 Day 1 from patients who received zimberelimab according to the schedule of assessments in Appendix Table 1.

6.8. Immunogenicity (Antidrug Antibodies)

Peripheral blood for immunogenicity assessments for ADAs against magrolimab and zimberelimab will be collected as described in the schedule of assessments (Appendix 2). 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 and anti-zimberelimab antibodies will be determined by a validated chemiluminescence immunoassay method.

6.9. Biomarker Assessments

Biomarker samples will be collected to assess PD, mechanism of action, and treatment response biomarkers and to define correlates of clinical efficacy and/or safety, as outlined in Section 3.8. The biomarker sample collection schedules are outlined in Appendix 2.

Patients are required to submit mandatory pretreatment tumor tissue from a core needle or excisional tumor biopsy (fine needle aspirate is not adequate) from a site not previously irradiated. 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 be requested to consent to a mandatory on-treatment 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 summarized in Appendix Table 2. There are 2 types of follow-up visit, as follows:

- Safety follow-up (30 days [± 7 days] after the last dose of study drug, or the start of subsequent therapy; or 90 days [± 7 days] after the last dose of zimberelimab, or the start of subsequent therapy, whichever occurs first)
- Survival follow-up (every 2 months after the safety follow-up)

Patients who discontinue study treatment are to return for an end-of-treatment 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 visit or telephone call 30 days (± 7 days) after their last dose of study treatment (or 90 days after the last dose of zimberelimab) or prior to the start of subsequent antineoplastic therapy, whichever occurs first. When an SAE or treatment-related AE is reported during a 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 5. Testing during preprogression visits and 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 or in person, as needed, every 2 months until death or the end of the study. Duration of survival follow-up will be limited to 5 years.

6.11. Assessments for Early Discontinuation From Study Treatment

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). In the absence of disease progression, scans should continue to be collected as described in Section 6.6 until disease progression or initiation of systemic antitumor therapy other than the study treatment, whichever is earlier. 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 are provided in Section 3.4.

6.12. Criteria for Discontinuation From Study/End of Study

Criteria for discontinuation from study are 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. Posttreatment assessments are described in Appendix Table 2. See Appendix 12 for poststudy care considerations in France.

6.14. Sample Storage

CCI [redacted] 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.)
- Inpatient 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 that 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 NCI CTCAE Grade 5.

7.1.3. Study Drugs and Gilead Concomitant Therapy Special Situations Reports

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

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

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

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

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

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

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

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

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

Counterfeit or falsified medicine is defined as any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

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

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

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

7.2.2. Assessment of Severity

The severity of AEs will be graded using the NCI CTCAE, Version 5.0. For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale (Appendix 4).

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study medication, only SAEs related to protocol-mandated procedures are to be reported, using the applicable eCRFs.

7.3.2. Adverse Events

Following initiation of study drug, all AEs, regardless of cause or relationship, will be collected until 30 days after last administration of study drug (or 90 days after the last administration of zimberelimab) or start of subsequent anticancer therapy, whichever occurs first and reported on the eCRFs as instructed.

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

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the initiation of the first dose of study drug and throughout the duration of the study, including the posttreatment follow-up visit, must be reported on the applicable eCRFs and to Gilead PS as instructed below in this section. Only SAEs that are considered related to study procedures are to be reported during the screening period.

Any SAEs and deaths that occur after the posttreatment follow-up visit but within 30 days of the last dose of study drug (or 90 days after the last dose of zimberelimab), regardless of causality, should also be reported.

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: Gilead PS
PPD
or
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.

Gilead: Gilead PS
PPD
or
PPD

7.4.2.2. Reporting Process for Gilead Concomitant Medications

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

Gilead: Gilead PS
PPD
or
PPD

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

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

7.4.2.3. Pregnancy Reporting Process

The investigator should report pregnancies in female study patients that 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.

In the zimberelimab-containing cohort only, the investigator should report pregnancies in female partners of male patients that are identified after initiation of study drug and throughout the study for 120 days after the last dose of zimberelimab 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: Gilead PS
PPD
or
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 should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy should be reported to Gilead PS using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PS. Gilead PS contact information is as follows:
email: PPD

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

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA CFR, 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 AEs, 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 AEs or SAEs 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, preexisting 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, as {U.S. Department of Health and Human Services 2009}:

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

7.8. Toxicity Management

7.8.1. Magrolimab

7.8.1.1. Type and Screen and Direct Antiglobulin Test

Magrolimab may interfere with RBC phenotyping due to expected coating of the RBC membrane. Due to the risk of developing anemia, and because magrolimab may make phenotyping difficult, at screening and prior to exposure to magrolimab, ABO/Rh type, antibody screen, DAT, and extended RBC phenotyping (including minor antigens such as CcDEe, Cw, MNSs, Kk, FyaFyb, and JkaJkb) will be performed for each patient (Section 6.4.2).

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

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

Magrolimab binds to RBCs and leads to erythrophagocytosis. CD47 is a member of the Rh complex in the RBCs 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. Significant drops in hemoglobin level (2 g/dL or higher) have also been observed in early doses. 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. 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.

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

For Patients After Exposure to Magrolimab:

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

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

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

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

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

7.8.1.3. Management of Infusion-Related Reactions

Infusion-related reactions are defined by the NCI CTCAE, Version 5.0 as “a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances” (Appendix 4). For the purposes of this study, the time frame for IRR assessment is the 24-hour period beginning at the start of the infusion. Premedications as described in Section 5.9.2 will be used to proactively manage IRRs.

Recommendations for the management of IRRs are provided in Table 21.

Table 21. Management of Infusion-Related Reactions

Infusion-Related Reactions	
CTCAE Grade	**Management**
Grade 1 Mild transient reaction	Remain at bedside and monitor patient until resolution of 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/placebo 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/placebo 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. Patients who experience a Grade 2 IRR 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/placebo. 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. 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. 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 will be permanently discontinued from the study treatment. For anaphylaxis, investigators should follow their institutional guidelines for treatment.

Infusion-Related Reactions	
CTCAE Grade	**Management**
	All patients with a Grade 3 or higher IRR will be observed until the AE resolves or stabilizes, with vital sign measurements and additional evaluations as medically indicated for the management of the AE.

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

7.8.1.4. Management of Pneumonitis

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

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

Management of potential pneumonitis is detailed in Table 22 and follows American Society of Clinical Oncology guidelines for immune-related AEs {Brahmer 2018}. Patients who experience Grade 3 or 4 pneumonitis will be permanently discontinued from study treatment.

Table 22. Pneumonitis Management Algorithm

CTCAE Grade of Pneumonitis	Management	Follow-Up
Grade 1 Radiographic changes (chest x-ray or CT) only	Monitor for signs and symptoms weekly and consider monitoring with chest x-ray Consider pulmonary and infectious disease consults	Consider reimaging with CT in 3 to 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 to 3 days; consider hospitalization 1 mg/kg/day oral prednisone or IV equivalent Consider bronchoscopy, lung biopsy	Reimage every 1 to 3 days If improving to baseline, taper corticosteroids over 4 to 6 weeks and resume magrolimab therapy per protocol If no clinical improvement after 48 to 72 hours or worsening, treat as Grade 3 to 4
Grade 3 or 4 Severe new symptoms; new/worsening hypoxia; life-threatening	Discontinue magrolimab therapy Hospitalize Pulmonary and infectious disease consults 1 to 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 to 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; IV = intravenous

7.8.1.5. Thromboembolic Events

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

7.8.1.6. Severe Neutropenia

Severe neutropenia and febrile neutropenia have been reported in patients treated with magrolimab. Close monitoring of hematologic parameters (Table 20) including neutrophils is required for all patients treated with magrolimab. Prophylactic antibiotics and/or antimycotics should be considered. Administer G-CSF if clinically indicated.

Recommendations for magrolimab dose delay in case of severe neutropenia:

- For Grade 3 neutropenia (ANC ≥ 500 cells/µL) without fever or infection, delay of magrolimab dosing is not recommended.
- For Grade 4 neutropenia (ANC < 500 cells/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.

7.8.1.7. 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 or more days, consider discontinuation of magrolimab.

7.8.2. Pembrolizumab

Dose modifications for pembrolizumab are described in Section 5.10.1.

Adverse events associated with pembrolizumab exposure may represent an immune-based etiology. These immune-related AEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment are critical to reduce complications. Based on existing clinical study data, most immune-related AEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected immune-related AEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and skin biopsy may be included as part of the evaluation. Based on the severity of immune-related AEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab are provided in Table 23. If pembrolizumab is discontinued for reasons other than disease progression, the remaining drug(s) in the combination regimen may be continued. Additional safety guidelines are provided in the country-specific prescribing information.

Table 23. Pembrolizumab Dose Modification and Toxicity Management Guidelines

Immune-Related AE	Toxicity Grade or Conditions (CTCAE Version 5.0)	Action Taken With Pembrolizumab	Immune-Related AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor patients for signs and symptoms of pneumonitis • Evaluate patients with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue		
Diarrhea/colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor patients for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Patients with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Patients with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Grade 4	Permanently discontinue		
AST/ALT elevation or increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of prednisone 0.5-1 mg/kg or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of prednisone 1-2 mg/kg or equivalent) followed by taper	
T1DM or hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for patients with T1DM • Administer antihyperglycemic in patients with hyperglycemia	• Monitor patients for hyperglycemia or other signs and symptoms of diabetes

Immune-Related AE	Toxicity Grade or Conditions (CTCAE Version 5.0)	Action Taken With Pembrolizumab	Immune-Related AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[a]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[a]		
Hypothyroidism	Grades 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE, administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/persistent Grade 2	Withhold	• Based on type and severity of AE, administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include, and are not limited to, GBS and encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; GBS = Guillain-Barre Syndrome; GI = gastrointestinal; IV = intravenous; T1DM = type 1 diabetes mellitus

a The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

For patients with Grade 3 or 4 immune-related endocrinopathy for which withholding of pembrolizumab is required, pembrolizumab may be resumed when the AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieves metabolic control (in the case of type 1 diabetes mellitus [T1DM]).

7.8.3. Zimberelimab

Zimberelimab management guidelines are provided in Table 24, which is intended to provide guidance on how to manage zimberelimab (eg, continue treatment, hold treatment, resume treatment, permanently discontinue) for a given toxicity. Monitor patients closely for signs and symptoms of immune-related AEs. Early evaluations with radiographic imaging, relevant laboratory testing, procedures and specialty consultation should be considered. Management of toxicities should be conducted in accordance with best clinical practices, standard institutional guidelines, and current European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), and/or National Comprehensive Cancer Network (NCCN) guidelines. The study medical monitor may be contacted if there are differences between these toxicity management guidelines and local guidelines and/or institutional standard practice. Additional country-specific requirements for monitoring of zimberelimab toxicity are presented in Appendix 12 (patients in Belgium only).

All toxicities will be graded according to NCI CTCAE Version 5.0. In case of doubt, the investigator should consult with the medical monitor.

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

Table 24. Treatment Modifications and Toxicity Management for Zimberelimab

Adverse Event	Severity	Action to be Taken With Zimberelimab
Infusion-related reaction (including anaphylaxis)	Grade 1-2	• Interrupt infusion • If symptoms resolve with supportive care promptly consider resuming infusion [redacted]
	Grade 3-4 (including anaphylaxis)	• Stop infusion and permanently discontinue
Dermatologic toxicity (including but not limited to rash, maculopapular rash, and pruritis) For SJS and TEN, see specific recommendations	Grade 1	• Continue at investigator discretion
	Grade 2-3	• Consider holding • If treatment is held, resume when improved to Grade 1 or baseline
	Grade 4	• Permanently discontinue
SCAR (including but not limited to SJS or TEN)	Any	• Permanently discontinue
Myocarditis	Grade 2-4	• Permanently discontinue

Adverse Event	Severity	Action to be Taken With Zimberelimab
Hepatitis/transaminitis without elevated bilirubin	Grade 2	• Withhold • If held, resume after ALT/AST returns to baseline
	Grade 3 or 4	• Permanently discontinue
Hepatitis/transaminitis with elevated bilirubin (except in Gilbert's syndrome)	Grade 1 or 2 blood bilirubin increased	• Withhold • Discontinue any potentially hepatotoxic medications. If no resolution, then permanently discontinue
	Grade ≥ 3 blood bilirubin increased	• Permanently discontinue
Endocrinopathies (adrenal, pituitary, diabetes)	Grade 1 or 2	• Consider holding
	Grade 3 or 4	• Hold until clinical management is stable • Resume when improved to Grade ≤ 1
Thyroid disorder (hypothyroidism and hyperthyroidism)	• No discontinuation required for hypothyroidism • For symptomatic hyperthyroidism resembling Graves-like disease, consider holding and resuming after workup is complete and there is evidence of improvement in symptoms and TFTs	
Nephritis or immune-mediated kidney injury	Grade 2	• Hold • Resume when improved to ≤ Grade 1 and steroids are tapered to ≤ 10 mg/day or discontinued
	Grade 3 or 4	• Permanently discontinue if related to treatment
Diarrhea/colitis including immune-mediated colitis/ enterocolitis	Grade 2 or 3	• Hold • Resume when colitis/diarrhea resolves to Grade ≤ 1 and steroid dose is stable/decreasing at ≤ 10 mg/day (prednisone or equivalent dose) • Discontinue if recurrence on rechallenge
	Grade 4	• Permanently discontinue
Pneumonitis, including immune-mediated lung disease and interstitial lung disease	Grade 1	• Monitor closely if continuing
	Grade 2	• Hold • Consider resuming when improved to Grade ≤ 1 and steroid dose is stable/decreasing at ≤ 10 mg/day (prednisone or equivalent dose)
	Grade 3 or 4 pneumonitis	• Permanently discontinue

Adverse Event	Severity	Action to be Taken With Zimberelimab
Pancreatitis	Grade 2	• Consider holding • Resume when: ○ Symptoms no longer present ○ No radiographic evidence of pancreatic inflammation ○ Amylase and lipase have returned to normal or baseline
	Grade 3 or 4	• Permanently discontinue
Other (may involve any organ system)	Grade 2	• Consider holding • If held, resume when improved to ≤ Grade 1
	Grade 3	• Hold • Consider resuming when improved to ≤ Grade 1
	Grade 3 (recurrent) or Grade 4	• Permanently discontinue

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SCAR = severe cutaneous adverse reaction; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; TFTs = thyroid function tests

7.8.4. 5-Fluorouracil

Safety management guidelines for 5-FU are described in Section 5.12.1. Additional safety guidelines are provided in the country-specific prescribing information.

7.8.5. Cisplatin

Safety management guidelines for cisplatin are described in Section 5.13.1. Additional safety guidelines are provided in the country-specific prescribing information.

7.8.6. Carboplatin

Safety management guidelines for carboplatin are described in Section 5.13.1. Additional safety guidelines are provided in the country-specific prescribing information.

7.8.7. Docetaxel

Safety management guidelines for docetaxel are described in Section 5.14. Additional safety guidelines are provided in the country-specific prescribing information.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The objectives and endpoints are provided in Section 2.

8.2. Planned Analyses

8.2.1. Safety Analysis

8.2.1.1. Dose Determination Analysis

For the purposes of making the dose de-escalation decisions for the safety run-in evaluations, 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 1 dosing cycle (21 days), as defined in Section 3.1.1.

8.2.2. Efficacy Analysis

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

8.2.2.1. Phase 2 Cohort 1

For Phase 2 Cohort 1, the primary analysis of PFS will be conducted after 93 PFS events occur in Arm A and Arm B.

8.2.2.2. Phase 2 Cohorts 2 and 3

For Phase 2 Cohorts 2 and 3, the primary analysis of ORR will be conducted 6 months after the last patient is enrolled.

8.2.3. Final Analysis

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

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Efficacy

8.3.1.1.1. Safety Run-in

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

8.3.1.1.2. Phase 2 Cohort 1

For Phase 2 Cohort 1, the primary analysis set for efficacy analysis is the Intent-to-Treat (ITT) Analysis Set, defined as concurrent randomized patients according to the treatment group to which the patients are randomized, unless otherwise specified.

8.3.1.1.3. Phase 2 Cohorts 2 and 3

For Phase 2 Cohorts 2 and 3, the primary analysis set for efficacy analysis is the mITT Analysis Set, defined as all patients who receive at least 1 dose of study drug.

8.3.1.2. Safety

8.3.1.2.1. Safety Run-in

For the safety run-in evaluations, the primary analysis set for the DLT analysis is the DLT-Evaluable Analysis Set, which will include all enrolled patients who meet either of the following criteria during the DLT assessment period:

- The patient experiences a DLT at any time after initiation of the first infusion of magrolimab.
- The patient does not experience a DLT and completes at least 2 infusions of magrolimab and at least 1 dose of pembrolizumab, 1 dose of platinum, and 1 dose of 5-FU for Safety Run-in 1; at least 1 dose of docetaxel for Safety Run-in 2; and at least 1 dose of pembrolizumab for the pre-expansion safety run-in for magrolimab + pembrolizumab (if applicable).

For the safety run-in evaluations, the primary analysis set for safety analyses other than the DLT analysis is the Safety Analysis Set, defined as all patients who receive at least 1 dose of study drug.

8.3.1.2.2. Phase 2 Cohort 1

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

8.3.1.2.3. Phase 2 Cohorts 2 and 3

For Phase 2 Cohorts 2 and 3, the analysis set for safety analyses is the Safety Analysis Set, defined as all patients who receive at least 1 dose of any study drug.

8.3.1.3. Pharmacokinetics

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

The PK analysis for zimberelimab may be conducted on the Zimberelimab PK Analysis Set when appropriate, defined as all patients who receive any amount of zimberelimab and have at least 1 measurable posttreatment serum concentration of zimberelimab.

8.3.1.4. Immunogenicity

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

The immunogenicity analysis for zimberelimab may be conducted on the Zimberelimab Immunogenicity Analysis Set when appropriate, defined as all patients who receive any amount of zimberelimab and have at least 1 evaluable anti-zimberelimab antibody test result.

8.3.1.5. Biomarker

The biomarker analysis will be conducted on the Biomarker Analysis Set, defined as all patients who receive 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, and 95% CIs for the mean, median, minimum, and maximum. Summary tables for categorical variables will include the following statistics: N, n, percentage, and 95% CIs for 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. For patients who were not dosed, unless otherwise specified, the baseline value will be the last (most recent) value before or on the randomization date (Phase 2 Cohort 1) or enrollment date (Safety Run-in cohorts and Phase 2 Cohorts 2 and 3). 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 treatments, tumor imaging for baseline response assessment, ECOG performance status, and randomization stratification factors (ie, PD-L1 expression and p16 status), if applicable.

8.5. Efficacy Analysis

8.5.1. Primary Efficacy Endpoint Analyses

8.5.1.1. Phase 2 Cohort 1

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

8.5.1.2. Phase 2 Cohorts 2 and 3

For Phase 2 Cohorts 2 and 3, the ORR along with the 95% CI based on the Clopper-Pearson method will be estimated. Patients who do not have sufficient baseline or on-study tumor assessment to characterize response will be counted as nonresponders.

8.5.2. Secondary Efficacy Endpoint Analyses

For Phase 2 Cohort 1, analyses of OS and PFS as secondary efficacy endpoints will be similar to that of the primary efficacy endpoint of PFS. For the analysis of ORR as the secondary efficacy endpoint, the ORR along with the 95% CI will be estimated based on the Clopper-Pearson method for each treatment group. The Cochran Mantel-Haenszel test adjusted for stratification factors will be used to compare treatment difference in ORR.

For Phase 2 Cohorts 2 and 3, analysis of ORR as the secondary efficacy endpoint will be similar to that of the primary efficacy endpoint of ORR. The OS and PFS as secondary efficacy endpoints will be analyzed using KM methods. The KM estimate of the median duration, its corresponding 95% CI, and the KM plots will be provided, when appropriate.

For analyses of DOR, the KM method will be used to estimate the median duration and its corresponding 95% CI, and the KM plots will be provided, when appropriate.

8.6. Safety Analysis

8.6.1. Primary Safety Endpoint Analysis

For the safety run-in evaluations, the incidence of DLTs during the DLT assessment period by count and percentage will be reported for each safety run-in using the DLT-Evaluable Analysis Set. The DLT assessment period is defined as the first cycle (21 days) and applies to each safety run-in evaluation.

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 plus 30 days (or plus 90 days after the last dose of zimberelimab) and prior to the day of initiation of subsequent antineoplastic therapy, will be summarized by cohort and treatment group (according to the study drug received). Data for the pretreatment and treatment-free safety follow-up periods will be included in data listings. For categorical safety data, including incidence of AEs and categorizations of laboratory data, the number and percentage of patients will be summarized. For continuous safety data, including laboratory data, the 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 drug data will be generated from the study drug administration data. Exposure data will be summarized by cohort and treatment group.

8.6.4. Adverse Events

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

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus 30 days (or 90 days after the last dose of zimberelimab) and prior to the day of initiation of subsequent antineoplastic therapy.

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

8.6.5. Laboratory Evaluations

Selected laboratory data (using conventional units) will be summarized using only observed data. 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 4.

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 last dose of study drug plus 30 days (or 90 days after the last dose of zimberelimab) and prior to the day of initiation of subsequent antineoplastic therapy for patients who permanently discontinue study drug, will be summarized by cohort and treatment group. If baseline data are missing, then any graded abnormality (ie, at least Grade 1) will be considered treatment emergent.

Laboratory abnormalities that occur before the first dose of study drug or after the patient has been discontinued from treatment for at least 30 days (or 90 days after the last dose of zimberelimab) and prior to the day of initiation of subsequent antineoplastic therapy will be included in a data listing.

8.6.6. Other Safety Evaluations

Other safety measures will be summarized by cohort and treatment group, when appropriate. 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 mean concentration versus time profiles by treatment will be generated. All data from this study may be combined with PK data from other Gilead clinical studies and analyzed using a population PK model. Such an analysis would be reported separately. If data allows, an exposure versus response (efficacy and/or safety) analysis may be conducted and reported separately. Pharmacokinetic analyses for zimberelimab may be performed and reported, as appropriate. Zimberelimab PK data from this study may be pooled with data from other studies to perform population PK analysis and will be reported separately.

8.8. Immunogenicity Analysis

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

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 the applicable sample collection time point by cohort and treatment group, as appropriate. CCI [redacted] Methods will be described in a separate Biomarker Analysis Plan.

8.10. Analysis of Patient-Reported Outcome Data

Changes from baseline in the EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D-5L questionnaires will be calculated.

8.11. Sample Size

For Phase 2 Cohort 1 Arm A versus Arm B, a total of 93 PFS events provides 75% power at a 1-sided alpha of 0.15 to detect an HR of 0.7 (assuming median PFS of 7 months compared with a control group median PFS of 4.9 months) using an unstratified log-rank test. Assuming an accrual period of 15 months, a minimum follow-up time of 5 months, and a 10% annual drop-out rate, 66 patients per treatment group (Arm A versus Arm B) would be required to obtain 93 events. Once the Phase 2 Cohort 1 enrolls 20 patients in each Arm A and Arm B, Arm C will

open. For Arm C versus Arm B, a total of 61 PFS events provides 64% power at a 1-sided alpha of 0.15 to detect an HR of 0.7 (assuming a median PFS of 7 months compared with a control group median PFS of 4.9 months) using an unstratified log-rank test. Assuming an approximate accrual of 11 months, a minimum follow-up time of 5 months, and a 10% annual drop-out rate, 46 patients per treatment arm (Arm C versus concurrent Arm B) would be required to obtain 61 events. The control group assumption is based on pembrolizumab + platinum + 5-FU efficacy in a historical study (KEYNOTE-048) {Burtness 2019}. The power calculation was performed using EAST 6.5.

For Phase 2 Cohort 2, no formal sample size calculation has been performed (25 patients).

For Phase 2 Cohort 3, a sample size of 40 patients provides 83% power at a 1-sided alpha of 0.15 to detect an ORR of 18% compared with a null ORR of 7.9% using a chi-squared test. The null ORR is based on historical taxane efficacy data in the second-line setting {Cohen 2019, Ferris 2016}. The power calculation was performed using 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 (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Gilead or proprietary interests in the study drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last 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. CCI [redacted] The results of the tests performed on the samples will not be given to the patient or the investigator.

9.1.5. Confidentiality

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

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

9.1.6. Study Files and Retention of Records

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

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

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

- Patient identification
- Documentation that patient meets eligibility criteria (ie, medical history, physical examination, and confirmation of diagnosis [to support inclusion and exclusion criteria])
- Documentation of the reason(s) a consented patient is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol

- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date, and including causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medication (start and end date; dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

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

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

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

9.1.7. Case Report Forms

For each patient consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the electronic data capture (EDC) system. The eCRF casebook will only capture the data required per the protocol schedules of assessments. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the CRF Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or Gilead staff who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. At a minimum, prior to 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 will be prepared and provided to the regulatory agency. 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.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.
- The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include Gilead's confidential information (Section 9.1.5).
- The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

CLINICAL STUDY PROTOCOL ACKNOWLEDGMENT

A Phase 2 Study of Magrolimab Combination Therapy in Patients with Head and Neck Squamous Cell Carcinoma

GS-US-548-5916 Amendment 6, 01 November 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. Schedules of Assessments

Appendix Table 1. Schedule of Assessments–Screening and Treatment Period

		Cycle (21-Day Cycles)								
		1[a]				2[a]			3[a]	4+[a]
Visit Window (Days)	**Screening**	**None**		**± 3[b]**		**± 3[b]**			**± 3[b]**	**± 3[b]**
Cycle Day	**Days −30 to −1**	**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									
Thyroid panel[b, h]	X					X				X, Q2C
Blood phenotyping or genotyping, type and screen (ABO/Rh), DAT	X									
Diagnostic Tissue Testing: PD-L1 and p16 HPV[i]	X									
Urinalysis[b, j]	X									
Tumor imaging[k]	X								X	X[k]
Tumor biopsy (all patients)	X								X[l]	
Adverse events[m, hh]	X	X	X	X	X	X	X	X	X	X
Concomitant medications[hh]	X	X	X	X	X	X	X	X	X	X
Randomization[n]	X									
PRO assessment: EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D-5L[b]		X				X			X	X

		Cycle (21-Day Cycles)								
		1[a]				2[a]			3[a]	4+[a]
Visit Window (Days)	**Screening**	**None**		**± 3[b]**		**± 3[b]**			**± 3[b]**	**± 3[b]**
Cycle Day	**Days −30 to −1**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**	**1**
Receptor occupancy[o]		X		X	X				X	X (C5 and C10)
Circulating tumor DNA[p]	X	X			X				X	X[p] (C5 and C10)
PBMC[q]		X		X	X	X			X	X[q] (C5)
Serum and plasma biomarkers[r, s]	X	X		X	X	X			X	X[r] (C5 and C10)
Whole blood RNA[r, s]		X		X	X	X			X	X[r] (C5 and C10)
Immunophenotyping assay[q, s]		X		X	X	X			X	X[q] (C5)
TCR sequencing[q]		X			X	X			X	X[q] (C5)
Stool microbiome[t]		X								
Whole blood genomic[u]		X								
PK (Magrolimab)[v, w]		X		X	X	X			X	X (C5 and C10)
PK (Zimberelimab)[x]		X							X	
Antidrug antibodies (Magrolimab)[y]		X				X			X	X
Antidrug antibodies (Zimberelimab)[z]		X							X	
IRT registration[aa]	X	X		X	X	X	X	X	X	X
All Cohorts, except Phase 2 Cohort 1 Arm B										
Premedication for magrolimab[bb]		X		X						
Magrolimab[cc]		X[f]		X[f]	X	X	X	X	X	X
Safety Run-in 1, Pre-expansion Safety Run-in for Magrolimab + Pembrolizumab (if Applicable), and Phase 2 Cohorts 1 and 2 Only:										
Pembrolizumab[dd]		X				X			X	X
Phase 2 Cohort 1 Arm C Only										
Zimberelimab[dd]		X				X			X	X
Safety Run-in 1 and Phase 2 Cohort 1 Only:										
Cisplatin or carboplatin[ee]		X				X			X	X (C4-6)
5-FU[ff]		X				X			X	X (C4-6)
Safety Run-in 2 and Phase 2 Cohort 3 Only:										
Docetaxel[gg]		X				X			X	X

5-FU = 5-fluorouracil; ABO = any of the 4 blood groups A, B, AB, and O comprising the ABO system; ADA = antidrug antibody; aPTT = activated partial thromboplastin time; C = Cycle; DAT = direct antiglobulin test; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire; EORTC QLQ-H&N35 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire – Head and Neck; EQ-5D-5L = 5-level EuroQol 5 dimensions; FT4 = free thyroxine; HPV = human papilloma virus; INR = international normalized ratio; IRT = interactive response technology; LDH = lactate dehydrogenase; PBMC = peripheral blood mononuclear cell; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetic(s); PRO = patient-reported outcome; PT = prothrombin time; PTT = partial thromboplastin time; Q2C = every 2 cycles; RECIST = Response Evaluation Criteria in Solid Tumors; Rh = rhesus; RP2D = recommended Phase 2 dose; T3 = triiodothyronine; TCR = T-cell receptor; TSH = thyroid-stimulating hormone

a In cases of magrolimab repriming following a treatment delay (Section 5.9.1), efficacy, biomarker, PK, and immunogenicity assessments should follow the schedule of the assigned cycle number. Magrolimab dosing and safety assessments should follow Cycle 1 (refer to Table 2 to Table 7, as appropriate) and then subsequently switch back to the assigned cycle schedule. 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 Cycle 3. Magrolimab should not be given on consecutive days. Refer to footnote (aa) for premedication requirement.

b Pretreatment assessments are to be collected within 24 hours (hemoglobin for the first 2 magrolimab doses per Section 7.8.1.2, PRO assessment) and within 3 days (safety labs) prior to any study treatment administration. For patients in Phase 2 Cohort 1 Arm B, assessments are not required at Cycle 1 Days 2, 8, and 15 and Cycle 2 Days 8 and 15.

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 on Day 1 of each cycle. For patients in Phase 2 Cohort 1 Arm B, vital signs are not required at Cycles 1 and 2 Days 8 and 15.

d A complete physical examination is to be performed at screening, and symptom-directed physical examinations are to be performed from Cycle 1 Day 1. For patients in Phase 2 Cohort 1 Arm B, physical examination is not required at Cycle 1 Days 8 and 15 and Cycle 2 Day 15.

e A serum pregnancy test will be conducted at screening. The Cycle 1 Day 1 urine pregnancy test does not need to be conducted if the screening pregnancy test was performed within 3 days before study treatment administration. Urine pregnancy tests will also be conducted at Cycle 2 Day 1 and every cycle thereafter.

f A complete blood count with differential, platelets, and reticulocytes will be conducted. For patients in Phase 2 Cohort 1 Arm B, samples are not required at Cycle 1 Days 2, 8, and 15 and Cycle 2 Days 8 and 15. Additional hemoglobin and hematocrit measurements will be performed 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment (Section 7.8.1.2).

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

h Thyroid tests to be completed are T3 (total or free), FT4, and TSH.

i PD-L1 results must be received prior to enrolling a patient in Phase 2 Cohorts 1 and 2. Known PD-L1 and p16 HPV results are acceptable providing protocol-specified assays were used for testing and results are available for source verification.

j Reflex microscopic testing based on other abnormalities.

k Computed tomography/magnetic resonance imaging/positron emission tomography-computed tomography (that includes a contrast-enhanced computed tomography component) will be performed per Section 6.6, every 6 weeks (2 cycles) until 36 weeks (Cycle 12) and then every 9 weeks (3 cycles) during the study (starting from Cycle 1 Day 1). Per RECIST criteria, 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.

l The Cycle 3 Day 1 tumor biopsy can be collected any time between Cycle 3 Day 1 and Cycle 4 Day 1.

m During screening, record only serious adverse events related to protocol-mandated procedures.

n Phase 2 Cohort 1 screening must be completed before randomization. Randomization must occur within 30 days of signing informed consent. The first dose of study treatment must be given within 3 business days after randomization.

o Receptor occupancy will be collected at select sites, only from patients assigned to receive magrolimab. Samples will be collected predose within 12 hours prior to receiving magrolimab. After Cycle 3, samples are to be collected on Day 1 of Cycles 5 and 10 and end of treatment, if occurring before Cycle 10.

p Circulating tumor DNA samples will be collected predose within 12 hours prior to any study treatment administration. After Cycle 3, samples are to be collected on Day 1 of Cycles 5 and 10 and at end of treatment. For patients in Phase 2 Cohort 1 Arm B, samples are not required at Cycle 1 Day 15.

q Samples will be collected predose within 12 hours prior to any study treatment administration. After Cycle 3, samples are to be collected on Day 1 of Cycle 5. PBMC and immunophenotyping assay samples will be collected at select sites. For patients in Phase 2 Cohort 1 Arm B, samples are not required at Cycle 1 Days 8 and 15.

r Samples will be collected predose within 12 hours prior to any study treatment administration. After Cycle 3, samples are to be collected on Day 1 of Cycles 5 and 10 and at end of treatment, if occurring before Cycle 10.
s For patients who receive magrolimab, an additional sample for serum and plasma biomarkers, whole blood RNA, and immunophenotyping assay will be collected 4 hours (± 30 minutes) after the start of administration of magrolimab on Cycle 1 Day 8.
t Stool microbiome to be collected predose on or before Cycle 1 Day 1.
u Whole blood genomic sample can be obtained at a subsequent visit if not obtained at Cycle 1 Day 1.
v On Cycle 3 Day 1, PK samples are to be collected predose (within 12 hours prior to magrolimab administration) and at 1 hour (± 15 minutes) after the end of infusion of magrolimab.
w Samples for magrolimab PK assessments are to be collected within 12 hours prior to magrolimab administration on Day 1 of Cycles 1, 2, 3, 5, and 10; on Days 8 and 15 of Cycle 1; and at end of treatment.
x Samples for zimberelimab PK assessments are to be collected within 12 hours prior to magrolimab administration and at the end of infusion (+15 minutes) on Day 1 of Cycles 1 and 3.
y Samples for magrolimab ADA assessments are to be collected within 12 hours prior to magrolimab administration on Day 1 of Cycles 1, 2, 3, 5, 10, and at the end of treatment.
z Samples for zimberelimab ADA assessments are to be collected within 12 hours prior to magrolimab administration on Day 1 of Cycles 1 and 3.
aa Interactive response technology registration will be required for screening, enrollment/randomization, and when dispensing any study drug supplied by Gilead Sciences.
bb Premedication with acetaminophen, diphenhydramine, and dexamethasone, or a comparable regimen, is required prior to the administration of the first 2 doses of magrolimab and in case of reintroduction with repriming (Section 5.9.2).
cc Magrolimab will be administered first before pembrolizumab or zimberelimab, cisplatin/carboplatin, 5-FU, and docetaxel. Patients should be monitored for 1 hour after infusion during Cycle 1. Postinfusion monitoring should begin after the infusion is complete but prior to administering any other study drug. Postinfusion monitoring is not required for doses after Cycle 1 Day 15.
dd Pembrolizumab or zimberelimab will always be administered after magrolimab. Pembrolizumab or zimberelimab may be administered on Day 2 of each cycle at the investigator's discretion for administrative reasons or to accommodate the patient's schedule.
ee Cisplatin or carboplatin will always be administered after magrolimab and pembrolizumab. To accommodate the patient's schedule, platinum chemotherapy may be dosed on Day 2 of each cycle at the investigator's discretion.
ff 5-Fluorouracil will always be administered after magrolimab, pembrolizumab or zimberelimab as a continuous intravenous infusion over 4 days. To accommodate the patient's schedule, 5-FU may be dosed on Day 2 of each cycle at the investigator's discretion.
gg Docetaxel will be administered after magrolimab.
hh For patients in Phase 2 Cohort 1 Arm B, adverse event and concomitant medication assessments at Cycle 1 Days 2, 8, and 15 and Cycle 2 Days 8 and 15 may be completed via phone call.

Refer to Appendix 12 for zimberelimab monitoring requirements in Belgium.

Appendix Table 2. Schedule of Assessments – Posttreatment

	EOT Visit	Safety Follow-Up Visit/Call[a]	Preprogression Visit[c]	Survival Follow-Up/Call
	Within 7 Days After Last Dose or EOT Decision	30 Days[b] After Last Dose	After Safety Follow-Up Until Disease Progression	Every 2 Months After Safety Follow-up Until Death or End of Study
Visit Window	**± 7 Days**	**± 7 Days**	**—**	**± 7 Days**
Urine pregnancy test[d]	X	X	X	X
Hematology[e]	X			
Serum or plasma chemistry	X			
Receptor occupancy[f]	X			
Circulating tumor DNA	X			
Serum and plasma biomarkers[f]	X			
Whole blood RNA[f]	X			
Pharmacokinetics	X			
Antidrug antibodies	X			
Tumor imaging for response assessment[g]	X		X	
ECOG	X			
Vital signs	X			
Symptom-directed physical examination	X			
PRO assessment	X			
Adverse events[h]	X	X		
Concomitant medications	X	X		
New anticancer therapy		X	X	X[i]
Survival follow-up				Q2M[j]

AE = adverse event; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; PRO = patient-reported outcome; Q2M = every 2 months; SAE = serious adverse event

a If the patient experiences a treatment-related AE or an SAE (regardless of attribution), the patient must be asked to come to the site. Visit may be conducted by telephone or in person.
b And at 90 days after the last dose for patients who receive treatment with zimberelimab or prior to the start of subsequent antineoplastic therapy, whichever occurs first.
c This will only apply for patients who stop study treatment in the absence of disease progression and who will continue to have tumor imaging. See footnote (g) for details on tumor imaging schedule. Preprogression visits will be completed first before proceeding to survival follow-up.
d Pregnancy testing will continue monthly up to 6 months after the end of treatment per the duration of required contraception, as discussed in Appendix 5. Testing during preprogression visits and survival follow-up may be done at home and the result self-reported by the patient.
e A complete blood count with differential, platelets, and reticulocytes will be conducted.
f Samples are to be collected at the end of treatment, if occurring before Cycle 10.
g Tumor imaging at the EOT visit is not required if performed within the last 30 days or progressive disease has been documented. Computed tomography/magnetic resonance imaging/positron emission tomography-computed tomography (that includes a contrast-enhanced computed tomography component) will be performed per Section 6.6. For patients who stop study treatment in the absence of disease progression (eg, experienced unexpected toxicity), scans should continue to be collected approximately every 6 weeks (2 cycles) until 36 weeks (12 cycles) from Cycle 1 Day 1 and then every 9 weeks (3 cycles) until disease progression or initiation of systemic antitumor therapy other than the study treatment, whichever is earlier.
h Report all AEs through the safety follow-up visit/call and any treatment-related SAEs thereafter.
i Collect new anticancer therapy data following the last dose of study treatment until the end of survival follow-up.
j Survival follow-up will be conducted via a phone call or in person, as needed, every 2 months until death or end of study. Duration of survival follow-up will be limited to 5 years.

Refer to Appendix 12 for zimberelimab monitoring requirements in Belgium.

Appendix 3. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with patients being unable to attend study visits have been identified for this study. Special pandemic measures can be applied only when these are 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 a virtual visit. 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 will not be able to stay on the study drug as planned per protocol.

            Mitigation plan: If permitted by local ethics committee (EC)/institutional review board (IRB), non-investigational product as determined by the sponsor (ie, pembrolizumab, 5-fluorouracil, platinum, or 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 alternative clinic.
    c) General patient selection guidance:
        i) To minimize patients receiving red blood cell transfusions, Gilead Sciences recommends selecting patients with higher hemoglobin thresholds at baseline and using 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 study patients is important, and testing of COVID-19 will be based on local clinical guidelines for testing based on signs/symptoms and/or suspected exposure to COVID-19.

Mitigation plan: If a patient has a diagnosis of COVID-19 while participating in 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 during the study will be performed in accordance with local institutional guidelines. Patients who are diagnosed with COVID-19 while participating in this clinical study will have this event documented as an AE 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 that cannot be mitigated due to the escalation of a pandemic, enrollment/randomization of new patients will be placed on hold until the pandemic outbreak is under control by following local regulatory guidelines.

Appendix 4. Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

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

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female-born patient is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal, unless the patient is permanently sterile or has medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 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 embryo-fetal 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 its mechanism of action and consistent with the risks identified for the approved anti-PD-1 agents, nivolumab and pembrolizumab, zimberelimab may cause fetal harm when administered to a pregnant woman. No contraindication to hormonal contraception is described in the zimberelimab investigator's brochure. Refer to the latest version of the investigator's brochure for additional information.

Based on its mechanism of action, pembrolizumab can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Advise women of the potential risk to a fetus. There is no contraindication to hormonal contraception according to the pembrolizumab prescribing information.

Based on the mechanism of action, 5-FU can cause fetal harm when administered to a pregnant woman. In animal studies, administration of 5-FU at doses lower than a human dose of 12 mg/kg caused teratogenicity. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. There is no contraindication to hormonal contraception according to the 5-FU prescribing information.

Based on human data from published literature, cisplatin for injection can cause fetal harm when administered to pregnant women. Data demonstrate transplacental transfer of cisplatin. Exposure of pregnant women to cisplatin-containing chemotherapy has been associated with oligohydramnios, intrauterine growth restriction, and preterm birth. Cases of neonatal acute respiratory distress syndrome, cytopenias, and hearing loss have been reported. Cisplatin for injection administration to animals during and after organogenesis resulted in teratogenicity. There is no contraindication to hormonal contraception according to the cisplatin prescribing information.

Based on animal studies, carboplatin has been shown to be embryotoxic and teratogenic in rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. There is no contraindication to hormonal contraception according to the carboplatin prescribing information.

Based on the mechanism of action and findings in animals, docetaxel can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant during therapy with docetaxel. If the 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 urine pregnancy test is required prior to study treatment administration on Cycle 1 Day 1. The Cycle 1 Day 1 urine pregnancy test does not need to be conducted if the screening pregnancy test was performed within 3 days before study treatment administration. Urine pregnancy tests will also be performed at Cycle 2 Day 1 and every cycle thereafter (described in the protocol) and continue monthly up to 6 months after the end of treatment per the duration of required contraception.

Duration of required contraception for female patients in this clinical study should start from the screening visit until 6 months after the last dose of the latest administered study drug unless there is a longer time requirement described in the country-specific prescribing information. If the duration of contraception differs by study drug, the longest effective duration of contraception should be observed.

Female 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 combined contraceptive patch

    ■ Combined contraceptive vaginal ring

    ■ Progesterone-only 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 unless there is a longer time requirement described in the country-specific prescribing information. If the duration of contraception differs by study drug, the longest effective duration of contraception should be observed. If the female partner of childbearing potential is not pregnant, use of any locally approved contraceptive measure should also be considered.

Male patients must also refrain from sperm donation and cryopreservation of cells during treatment and until the end of contraception requirement. If needed, male patients should be advised to seek advice about sperm donation and cryopreservation prior to treatment.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Female patients will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study to 6 months after last study drug dose. Study drug must be discontinued immediately.

Male patients whose partner has become pregnant or suspects she is pregnant from start of study to 6 months after last study drug dose must also report the information to the investigator. Partner pregnancy information will only be collected for the zimberelimab cohort in this study (throughout the study and for 120 days after the last dose of zimberelimab); however, the investigator should reinforce proper contraception use with the study patient if a partner pregnancy is reported in any cohort.

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

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

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

Appendix 7. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Head and Neck Module (EORTC QLQ-H&N35)

https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-HN35-English.pdf

Appendix 8. 5-Level EuroQol 5 Dimensions Questionnaire (EQ-5D-5L)

Health Questionnaire

English version for the UK

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

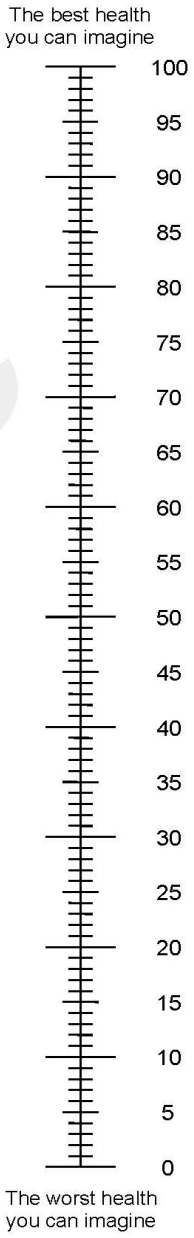
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



Appendix 9. 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 house work, 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 10. Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.1)

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

Appendix 11. Adapted Immune-Related Response Evaluation Criteria in Solid Tumors (irRECIST) Criteria

Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH et al. Developing a Common Language for Tumor Response to Immunotherapy: Immune-related Response Criteria using Unidimentional measurements. Clin Cancer Res. 2013; 19(14):3936–3943.

Appendix 12. Country-Specific Considerations

Appendix Table 3. France

Protocol Section	Consideration for France Only
Sections 3.6 and 6.13 (Poststudy care)	The sponsor will continue to provide magrolimab to patients, free of charge, for 3 years after completion of the study, subject to the following conditions: • The physician in charge of the study recommends that is in the best interest of the study patient to continue treatment with the study drug. • There is no suitable alternative medical treatment according to the Institutional Committee's decision. For patients receiving zimberelimab, an alternative, approved PD-1 inhibitor such as pembrolizumab may be substituted. The sponsor will be exempt from providing the study drug after the study is completed in one of the following cases: • The product development has been discontinued or the clinical studies with the product ended unsuccessfully. • Administering the study drug for prolonged period of time is unsuitable for the patient and may harm the patient's health. • When the study drug receives marketing authorization in the European Union in the indication under investigation in this study.

Appendix Table 4. Belgium

Protocol Section	Consideration for Belgium Only
Schedule of Assessments Tables (Appendix Table 1 and Appendix Table 2) Section 6.4.6 Section 7.8.3	Additional cardiac assessments for patients dosed with zimberelimab are added to study visits (see below).

On-Treatment Cardiac Monitoring Assessments

	Screening Days −30 to −1	Cycle (21-Day Cycles)								
		1				2			3	4+
Visit Window (Days)		None		± 3		± 3			± 3	± 3
Cycle Day		1	2	8	15	1	8	15	1	1
Troponin I[a]	X	As clinically indicated								
12-lead ECG[b]	X	As clinically indicated				X	As clinically indicated		As clinically indicated	X

ECG = electrocardiogram
a Additional cardiac biomarkers such as creatine kinase isoenzyme, brain natriuretic peptide, etc may be performed as clinically indicated. Assessments to be performed at the local laboratory.
b 12-lead ECG to be performed at screening, Cycle 2 Day 1, Cycle 4 Day 1, then every 4 cycles. Additional ECG assessments may be performed as clinically indicated.
In cases of suspected myocarditis, refer to Section 7.8.3, Table 24 and the international guidelines for recommendations on diagnostic tests and management including but not limited to cardiologist consultation, and cardiac functional tests such as echocardiography or cardiac magnetic resonance imaging as clinically indicated.

Posttreatment Cardiac Monitoring Assessments

	EOT Visit	Safety Follow-up Visit/Call	Preprogression Visit	Survival Follow-Up/Call
	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 Until Death or End of Study
Visit Window	**± 7 Days**	**± 7 Days**	—	**± 7 Days**
Troponin I[a]	X	X		
12-lead ECG[b]	X	X		

ECG = electrocardiogram; EOT = end of treatment

a Additional cardiac biomarkers such as creatine kinase isoenzyme, brain natriuretic peptide, etc may be performed as clinically indicated. Assessments to be performed at the local laboratory.

b 12-lead ECG to be performed at EOT and 30-day safety follow-up visit. Additional ECG assessments may be performed as clinically indicated.

In cases of suspected myocarditis, refer to Section 7.8.3, Table 24 and the international guidelines for recommendations on diagnostic tests and management including but not limited to cardiologist consultation, and cardiac functional tests such as echocardiography or cardiac magnetic resonance imaging as clinically indicated.

Appendix 13. Authorization Status of Study Interventions

Study Intervention Name	Category	Authorized in at Least 1 Country Following EU Regulation No. 536/2014	To Be Used per Label (Marketed Products Only)
Magrolimab	Study drug	No[a]	NA
Zimberelimab	Study drug	No[a]	NA
Pembrolizumab	Study drug	Yes	Yes
5-Fluorouracil	Study drug	Yes	Yes
Carboplatin	Study drug	Yes	Yes
Cisplatin	Study drug	Yes	Yes
Docetaxel	Study drug	Yes	Yes
Acetaminophen	AxMP	Yes	Yes
Diphenhydramine	AxMP	Yes	Yes
Dexamethasone	AxMP	Yes	Yes

AxMP = auxiliary medicinal product; EU = European Union; NA = not applicable
a Rationale described in Section 1.

Appendix 14. Amendment History

A high-level summary of this amendment is provided in tabular form in Appendix Table 5 with changes listed 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 5 to this amendment will be made available upon the publication of this protocol.

Appendix Table 5. Amendment 6 (01 November 2023)

Rationale for Key Changes Included in Amendment 6	Affected Sections
Nonclinical and clinical experience with zimberelimab was added to provide a rationale for the use of zimberelimab in Cohort 1 Arm C.	Sections 1.4 and 1.6
Objectives and endpoints were modified to indicate that disease progression will be determined by investigator assessment instead of independent central review.	Synopsis, Sections 2 and 3.1.2.1
Instructions outlining the duration of postinfusion monitoring of patients after zimberelimab infusion have been added to align with the pharmacy instructions for zimberelimab.	Section 5.11
Instructions on the administration of docetaxel have been added to allow for the infusion duration to follow local practice.	Section 5.14
The benefit/risk assessment of the study was updated with potential overlapping toxicities and their mitigation per the current clinical experience with magrolimab.	Section 1.6
New sections for management of severe neutropenia and serious infections have been added. Cross-references to these sections have been added for further clarity on magrolimab dose delays with regards to these adverse events.	Sections 5.9.1, 7.8.1.6, and 7.8.1.7
Guidance for the management of IRRs has been updated.	Sections 1.2.3.2 and 7.8.1.3
Guidance for the management of zimberelimab toxicities has been updated.	Section 7.8.3
Criteria for permanent discontinuation of magrolimab has been updated to include recurrent Grade 3 IRRs despite premedication.	Section 5.9.1
A new segment of text was added to accommodate patient schedules regarding the administration of pembrolizumab, zimberelimab, and platinum chemotherapy.	Section 5.16 and Appendix Table 1
Details for red blood cell phenotyping were added to clarify testing requirements.	Section 7.8.1.1
Text was updated for the monitoring and mitigation of anemia in patients with low baseline hemoglobin levels.	Section 7.8.1.2
Patient response assessments for secondary efficacy endpoints were updated to use Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 in order to align with the table of objectives and endpoints.	Section 6.6

Rationale for Key Changes Included in Amendment 6	Affected Sections
Information on study auxiliary medicinal products/noninvestigational medicinal products has been added.	Section 1.3.11
A new segment of text outlining standard-of-care (SOC) procedures, performed prior to obtaining informed consent, was added to clarify that certain SOC assessments are allowed to be used for patient eligibility at the screening period.	Section 6.2.1
Exclusion criteria 24 and 26 were updated to remove "systemic" for clarity.	Synopsis and Section 4.3
Exclusion criterion 22 was modified to allow patients with HIV who have undetectable HIV viral load to enroll.	Synopsis and Section 4.3
A sentence was added to clarify that questionnaires should be completed before any other study procedures with the exception of imaging and laboratory analyte assessments. A new sentence was also added to outline the exemptions for the completion of patient-reported outcomes (PRO) instruments if unavailable in patient's language or other barriers.	Section 6.4.7
Country-specific considerations for Belgium have been added. References to the country-specific requirements appendix have also been added throughout the document, as applicable.	Sections 6.4.6, 6.5, Appendix Table 1, Appendix Table 2, and Appendix 12
Appendix Table 1 footnote 'm' was updated to only record serious adverse events related to protocol-mandated procedures during screening.	Appendix 2
Text updated to allow local sourcing of commercial product when aligned with local regulations.	Sections 5.3.2, 5.5.2, 5.6.2, 5.7.2, and 5.8.2
An Authorization Status of Study Interventions table was added.	Appendix 13
Text clarifying the baseline value for patients who were not dosed was added.	Section 8.3.2
Text describing magrolimab contraindication in pregnancy has been updated to include nonclinical observations in embryo-fetal development.	Appendix 5
The reference for the Immune-Related Response Evaluation Criteria in Solid Tumors (irRECIST) Criteria has been updated.	Appendix 11
Global Patient Safety (GLPS) has changed to Patient Safety (PS) to reflect the new department name.	Throughout the protocol, as required
Minor changes were included to correct typographic errors.	Throughout the protocol, as required

Protocol GS-US-548-5916 Amend 6

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	02-Nov-2023 12:21:34