PROTOCOL TITLE: Phase II trial of magrolimab and cetuximab with pembrolizumab or docetaxel for recurrent/metastatic head neck squamous cell carcinoma

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Summary of Changes from Previous Version

Affected Section(s)	Summary of Revisions Made	Rationale
5.5	Removal of DLT	For compliance issues
3.2	Modification of Cohort B	For compliance
9.2	Sample Size Determination	For budget compliance

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LIST OF ABBREVIATIONS

ADA	Anti-drug Antibody
AE	Adverse Event
ALT	Alanine Aminotransferase/ Serum Glutamic Pyruvic Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase/ Serum Glutamic Oxaloacetic Transaminase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CD47	Cluster of Differentiation 47
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
IB	Investigator's Brochure
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenously
mAb	Monoclonal Antibody
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PD	Progression of Disease
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event

SD	Stable Disease
SIRP-α	Signal Regulatory Protein Alpha
SOC	Standard of Care
ULN	Upper Limit of Normal
WBC	White Blood Cells

STUDY SCHEMA

Eligibility	Arms	Staggered Phase*	Induction phase	Maintenance phase
R/M HNSCC ECOG PS 0-1 PD-L1 CPS	**ARM A** 1st line PD-1i naïve	Magro (Q1W) + Pembro (Q3W) x 1 cycle (3 wks)	Magro (Q1W) + Pembro (Q3W) + Cetux (Q1W) x 1 cycle (3 wks)	Magro + Cetux (Q2W) + Pembro (Q6W) (1 cycle = 6 wks)
	ARM B 2nd /3rd line PD-1i refractory	Magro (Q1W) + Cetux (Q1W) x 1 cycle (3 wks)	Magro + Cetux (Q1W) + Doce (Q1W) x 2-4 cycles (3 wks)	Magro+ Cetux (Q2W) (1 cycle = 6 wks)

Magro: magrolimab; Pembro: pembrolizumab, Cetux: cetuximab; Doce: docetaxel
* Staggered phase will be implemented during the safety run-in (6-12 patients in each Arm); after the safety run-in, if there is no increase in risk of infusion related reactions, the staggered phase may be eliminated.

1 INTRODUCTION

1.1 Study Rationale

Magrolimab is a first-in-class recombinant humanized mAb targeting the CD47-SIRP-α axis. Binding of magrolimab to human CD47 on-target malignant cells blocks the "don't eat me" signal to macrophages and enhances tumor cell phagocytosis. In addition, magrolimab has the potential to elicit an antitumor T-cell response. In pre-clinical studies, strong synergistic antitumor activity was demonstrated when magrolimab is combined with EGFR antibodies with Fc receptor-mediated immune effector activity, such as cetuximab. Furthermore, the combination of magrolimab with T-cell checkpoint inhibitors such as pembrolizumab can lead to enhanced antitumor activity.

RESEARCH HYPOTHESIS

Cohort A (anti-PD-1 naïve): The combination of magrolimab, cetuximab and pembrolizumab will be safe and increase objective response rate (ORR) when compared to reported ORR with pembrolizumab single agent or pembrolizumab plus cetuximab in the first-line setting.

Cohort B (anti-PD-1 refractory): The combination of magrolimab, cetuximab, and docetaxel will increase ORR when compared to ORR with single agent cetuximab or docetaxel in patients who have progressed on first-line systemic therapy.

1.2 Background

1.2.1 Clinical Data with Cetuximab Plus Anti-PD1 in R/M HNSCC

HNSCC is the sixth most common cancer worldwide. In 2020, there were more than **850,000 cases leading to 440,000 deaths**, according to The Global Cancer Observatory. The prognosis

of patients with R/M HNSCC is generally poor. The current standard-of-care first line systemic therapy is pembrolizumab single agent for patients with PD-L1 expression CPS of at least 1% or pembrolizumab combined with platinum and 5-FU, irrespective of PD-L1 status; nevertheless, median OS is still only 13 months (1). Pembrolizumab single agent has an attractive toxicity profile but only benefits approximately 17% of patients. Cetuximab is a monoclonal antibody (mAb) that targets EGFR but also can elicit immune functions such as antibody-dependent cell-mediated cytotoxicity involving NK cells, T-cell recruitment to the tumor, and T-cell priming via dendritic cell maturation (2). Currently, it is used in second or third line, following progression on anti-PD1 and/or chemotherapy. While not specifically studied after progression on anti-PD1, the ORR with single agent cetuximab following progression on chemotherapy is 8-13% (3).

There are two phase II studies evaluating the safety and efficacy of cetuximab with anti-PD1 in R/M HNSCC; both showing encouraging activity and an attractive toxicity profile(4, 5). In a phase II trial of pembrolizumab and cetuximab in 33 patients with platinum refractory or ineligible R/M HNSCC, mostly with oral cavity primary treated in the first-line setting, the reported ORR was 45% (15/33), which compares favorably with the ORR of 17% achieved with pembrolizumab single agent in the same setting. The median DOR was of 14.9 months and median OS 18.4 months. SAEs were observed in 3 (9%) patients, all grade 3: two patients developed grade 3 mucositis and discontinued cetuximab only with clinical improvement, and one patient with grade 3 colitis discontinued both treatments (5).

On another phase II study investigating cetuximab and nivolumab in R/M HNSCC who had progressed on at least one line of systemic therapy, 51% of patients were PD-1 refractory and the ORR was 22.2% (10/43). The 1-year OS, the study primary endpoint, was 57% for patients not previously exposed to ICI versus 33% for those previously treated with anti-PD1. The most common grade 3 TRAE were fatigue (13%) and rash-acneiform (4.4%). The only grade 4 TRAE was cetuximab infusion reaction in 1 patient (2.2%)(4).

Summary table of clinical efficacy data of prospective studies evaluating pembrolizumab (pembro), pembro plus chemotherapy (chemo), and pembro plus cetuximab in the first-line setting.

1st line	Pembrolizumab	Pembrolizumab + Chemotherapy	Pembrolizumab + Cetuximab
ORR	17%	36%	45%
PFS	2.3 m	4.9 m	NA
OS	11.6 m	13 m	18.4 m

1.2.2 Clinical Data with Taxanes With or Without Cetuximab in 2nd Line or Beyond in R/M HNSCC

There is limited clinical data using taxanes as a single agent or in combination with cetuximab in R/M HNSCC who progressed after first line systemic therapy. Phase III studies using weekly docetaxel as the control arm in the HNSCC platinum-refractory setting have shown modest activity with an ORR of 6.2% (6). In two phase III randomized trials investigating anti-PD1 versus

standard of care (SOC) docetaxel, cetuximab or methotrexate in the second-line setting, the clinical outcomes to SOC therapy were: ORR 5.8-10%; PFS 2.3 months and OS = 5.1-7.1 months (7).

In first line, taxane and cetuximab has shown encouraging activity in one single-arm phase II study, rendering an ORR of 54%, PFS of 4.2 months and OS of 8.1 months (8). Similar results have been reported by small, retrospective studies. There is no prospective data with taxane-cetuximab combination in the platinum-refractory setting. Retrospective studies often include mixed patient populations, for instance, in a retrospective study including 42 patients with R/M HNSCC treated with paclitaxel and cetuximab, 40% were platinum-refractory and 38% were treated in the first-line setting; the reported ORR was 38%, with a median PFS of 3.9 months and OS of 7.6 months (9).

Platinum-refractory (PD-1 naive)	Cetuximab	Docetaxel	Cetuximab + taxane
ORR	8-13%	6.2 %	No prospective data; retrospective data with mixed population
PFS	2.3 m	2.1 m	
OS	5.9 m	6 m	

The results of the EXTREME trial investigating the addition of cetuximab to platinum-5-FU (10) suggests that cetuximab has an additive effect when combined with chemotherapy (ORR increased from 20 to 36%); therefore, given that the ORR to docetaxel is approximately 6% in the platinum-refractory setting and the ORR to cetuximab is 8-13% in the same setting, it is reasonable to assume that the ORR to the docetaxel cetuximab combination is approximately 20% in the second- or third- line setting for platinum-refractory patients.

For patients treated with anti-PD1 as a single agent in first-line, it is expected that the ORR to the platinum-cetuximab doublet will be higher (~ 35% based on retrospective series), but no prospective data is available (11, 12).

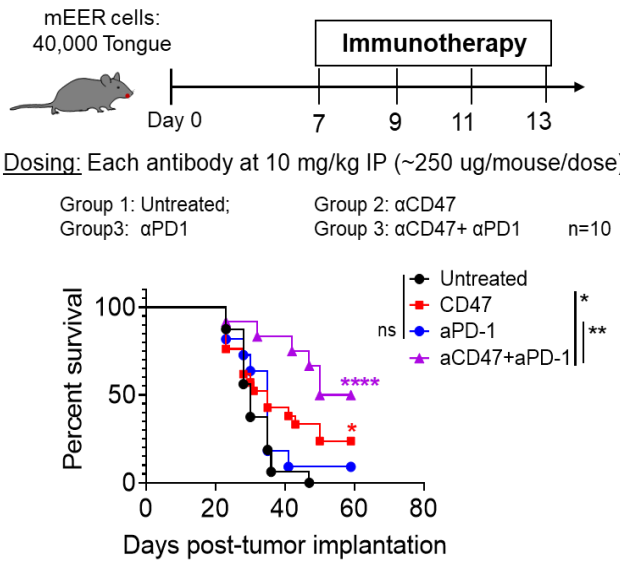
1.2.3 Targeting CD47 with Magrolimab and Combining with EGFR or PD1 inhibitor

Cluster of differentiation 47 (CD47) is a cell surface glycoprotein that inhibits phagocytosis by binding to the extracellular region of the inhibitory receptor signal regulatory protein alpha (SIRP-α) on macrophages, recognized as “do not eat me signal” (13). CD47 via its interaction with SIRPα, serves as a myeloid specific immune checkpoint, protecting the cancer cells from being recognized and cleared by macrophages (13, 14). In cancer cells, CD47 transcript and protein expression is aberrantly upregulated and is an independent predictor of poor prognosis in patients with various cancer types (13).

Magrolimab is a first-in-class recombinant humanized mAb targeting the CD47-SIRP-α axis. Binding of magrolimab to human CD47 on-target malignant cells blocks the “don’t eat me” signal to macrophages and enhances tumor cell phagocytosis. In addition, magrolimab has the potential to elicit an antitumor T-cell response.

In pre-clinical studies, strong synergistic antitumor activity was demonstrated when magrolimab is combined with EGFR antibodies with Fc receptor-mediated immune effector activity, such as cetuximab. Furthermore, the combination of magrolimab with T-cell checkpoint inhibitors such as pembrolizumab can lead to enhanced antitumor activity, which we have demonstrated in an HPV-positive oropharynx squamous cell carcinoma syngeneic mEER mouse model (unpublished data by Jagan Sastry PhD, Figure 1). CD47 blockade leads to tumor cell phagocytosis by macrophages and subsequent cross-presentation of tumor antigens by macrophages and other antigen presenting cells to CD8 T-cells, eliciting an adaptive immune cell response. Anti-PD-1 mAb enable enhanced T-cell activity by reversing T-cell exhaustion. Thus, the combination of magrolimab with an anti-PD-1 can lead to an enhanced T-cell antitumor response through these complementary mechanisms of action.

Fig. 1



*Single agent anti-CD47 showed partial but significant therapeutic benefit in the HPV+ tumor model
*There was synergistic therapeutic benefit when anti-CD47 was combined with anti-PD-1

mEER: mouse oral epithelial cells expressing HPV-16 E6 and E7 along with H-RAS. CCD47 is expressed by mEER tumor cells.

1.2.4 Magrolimab Clinical Pharmacology

Details of magrolimab clinical pharmacology and pre-clinical studies using magrolimab are available in the Investigator's brochure (IB). *In vitro* studies of magrolimab, showed high binding affinity to monomeric and bivalent human CD47 antigen with a dissociation constant (Kd) of 8×10^{-9} and 8×10^{-12} M, respectively. 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. 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.

Clinical pharmacokinetic (PK) have been analysed in all studies of magrolimab, alone or in combination, thus far. A nonlinear PK consistent with target-mediated clearance has been observed. Overall, 2-11% of patients tested positive for antidrug antibody (ADA) against magrolimab, however positivity had no impact on PK or clinical safety in these patients (SCI-CD47-001; SCI-CD47-002).

Preliminary PK data of magrolimab from other ongoing studies (5F9003, 5F9004, and 5F9005) indicate similar PK properties across all tumor populations and in the presence of co-administered drugs. 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.

1.2.5 Magrolimab Preliminary Clinical Data

The safety and preliminary activity of the combination of magrolimab with cetuximab is being evaluated in patients with solid tumors and colorectal cancer (SF9004). A total of 78 patients have been treated with this regimen and no dose limiting toxicities (DLTs) were identified (15).

The combination of magrolimab and the anti-PD-L1 avelumab is also being studied in solid tumors and ovarian cancer (SF9006) (16). Similarly, no DLTs were seen with the combination.

In both trials, cetuximab and avelumab standard doses are being used, with two maintenances doses of magrolimab being investigated: 30 and 45 mg/Kg.

The most common adverse events associated with magrolimab are fatigue (43%; 2.8% severe), anemia (40%, 22% severe), headache (36%; 1.4% severe), and infusion reactions (22%; 3.1% severe).

The main on-target toxicity of magrolimab is anemia, which does not overlap with cetuximab or anti-PD1; therefore, we envision the triplet will be well-tolerated. Magrolimab induced-anemia typically manifests as a decline in hemoglobin within the first 2 weeks of treatment followed by a compensatory reticulocytosis, with many patients experiencing a gradual return to baseline despite continued dosing. Administration of a low priming dose of magrolimab mitigated on-target anemia and will be utilized in this trial. Further details of completed and ongoing clinical trials investigating magrolimab as a single agent or in combination with other agents are available in the Investigator's brochure (IB).

1.3 Known Potential Risks

Please refer to Investigator's brochure (IB) for known potential risks of magrolimab from either clinical or nonclinical studies.

1.4 Correlative Studies Background

N/A

2 OBJECTIVES

2.1 Primary Objectives

Objective response rate (ORR) per RECIST v1.1

2.2 Secondary Objectives

- Adverse events rates per CTCAE V5.0 (appendix)
- Duration of response (DOR)
- Progression free survival (PFS) per RECIST v1.1
- Overall survival (OS) per RECIST v1.1

2.3 Exploratory Objectives

Assessment of blood and tissue-based biomarkers predictive of response to therapy

3 STUDY DESIGN

This is a two-arm, phase II, open-label study designed to evaluate the safety and activity of magrolimab, cetuximab, and pembrolizumab administered in first-line (cohort A) or magrolimab, cetuximab, and docetaxel administered in second or third line for PD-1-refractory (cohort B) R/M HNSCC patients. According to the United Stated prescribing information for pembrolizumab, Cohort A will only enroll patients with PD-L1 expressing tumors (combined positive score [CPS] ≥ 1); while cohort B will enroll patients irrespective of PD-L1 CPS status. The primary outcome is the ORR per RECIST v1.1 (17). The study will characterize the safety profile of the triplet therapies (safety run-in cohort). The efficacy will be evaluated by applying the Bayesian Optimal Phase 2 (BOP2) design {Zhou, 2017 #5879}

3.1 Cohort A

Anti-PD1 naïve patients will be administered concurrent systemic therapy with pembrolizumab 200 mg IV Q3W, cetuximab loading dose of 400 mg/m^2 followed by 250 mg/m^2 IV QW, and magrolimab 1mg/kg priming dose followed by weekly doses of 30 mg/Kg IV (Dose 0). Dose limiting toxicity (DLT) will be assessed during the first 2 cycles (6 weeks). If DLTs occur in > 2 out of the first 6 patients enrolled, magrolimab will be dose reduced as per Table 3. After 2 cycles of therapy (6 weeks), if objective response or stable disease is documented on scans, patients will be transitioned to the maintenance phase. To mitigate the risk of infusion-related reactions (IRR), a staggered phase will be implemented during the safety run-in (6-12 patients). As per Study Schema, during cycle 1, patients will receive magrolimab plus pembrolizumab; cetuximab will be added during cycle 2. After the safety run-in, if there is no increase in risk of IRR, the staggered phase may be eliminated.

3.2 Cohort B

Patients who have experienced cancer progression with anti-PD-1 as a single agent or combined with chemotherapy will be administered cetuximab loading dose of 400 mg/m^2 followed by 250 mg/m^2 IV QW, magrolimab 1 mg/Kg priming dose followed by maintenance doses of 30 mg/Kg IV QW, and weekly docetaxel 30 mg/m^2 IV QW (Dose 0). Docetaxel will be administered only for 6 to 12 weeks (2 to 4 cycles), followed by maintenance cetuximab and magrolimab doublet if objective response or stable disease is documented on scans after 2 to 4 cycles of the triplet therapy. If DLTs occur in > 2 out of the first 6 patients enrolled during the first 2 cycles (6 weeks), magrolimab will be dose reduced as per Table 3. To mitigate the risk of infusion-related reactions (IRR), a staggered phase will be implemented during the safety run-in (6-12 patients). As per Study Schema, during cycle 1, patients will receive magrolimab plus cetuximab; docetaxel will be added during cycle 2. After the safety run-in, if there is no increase in risk of IRR, the staggered phase may be eliminated.

Table 3. Magrolimab Dosing

3A.Magrolimab Dosing for Cohort A

Magrolimab 1 mg/Kg IV (3 hours ± 30 min)	Cycle (C) 1 Day (D) 1
Magrolimab starting dose level 30 mg/Kg IV (2 hours ± 30 min)	QW beginning at C1D8 and onward during the Staggered and Induction phases (5 weeks)
Magrolimab 30 mg/Kg IV (2 hours ± 30 min)	Q2W during the Maintenance phase (C3D1 onward)
Magrolimab de-escalation, Level -1 20 mg/Kg IV (2 hours ± 30 min)	QW beginning at C1D8 and onward during the Staggered and Induction phases (5 weeks) Q2W during the Maintenance phase (C3D1 onward)
Magrolimab de-escalation, Level -2 15 mg/Kg IV (2 hours ± 30 min)	QW beginning at C1D8 and onward during the Staggered and Induction phases (5 weeks) Q2W during the Maintenance phase (C3D1 onward)

3B. Magrolimab Dosing for Cohort B

Magrolimab 1 mg/Kg IV (3 hours ± 30 min)	Cycle (C) 1 Day (D) 1
Magrolimab starting dose level 30 mg/Kg IV (2 hours ± 30 min)	QW beginning at C1D8 and onward during the Staggered and Induction phases (8-14 weeks)

Magrolimab 30 mg/Kg IV (2 hours ± 30 min)	Q2W during the Maintenance phase
Magrolimab de-escalation, Level -1 20 mg/Kg IV (2 hours ± 30 min)	QW beginning at C1D8 and onward during the Staggered and Induction phases (8-14 weeks) Q2W during the Maintenance phase
Magrolimab de-escalation, Level -2 15 mg/Kg IV (2 hours ± 30 min)	QW beginning at C1D8 and onward during the Staggered and Induction phases (8-14 weeks) Q2W during the Maintenance phase

DLT Definition and Exceptions for Safety Run-in

A DLT for the safety run-in is defined as the occurrence of any ≥ Grade 3 toxicity (according to NCI-CTCAE v 5.0) with the exceptions below.

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) 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 1 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) and/or alkaline phosphatase.
- 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, pembrolizumab, or cetuximab 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 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.

• Grade 3 or 4 events clearly associated with the underlying disease, disease progression, concomitant medication, or comorbidity

Throughout treatment in Cohort A and B, dose reduction will be allowed for cetuximab, docetaxel and magrolimab due to treatment-related adverse events as outlined in the table below and detailed in section 5 “Treatment Plan”. There will be no dose adjustment for pembrolizumab. The use of prophylactic growth factor is allowed on Cohort B.

Table 4 Dose de-escalation for Safety Run-in

	Initial dose	Dose reduction 1	Dose reduction 2
Cetuximab Q1W	250 mg/m2	200 mg/m2	150 mg/m2
Cetuximab Q2W	500 mg/m2	400 mg/m2	300 mg/m2
Docetaxel Q1W	30 mg/m2	25 mg/m2	20 mg/m2
Magrolimab Q1W	30 mg/Kg	20 mg/Kg	15 mg/Kg
Magrolimab Q2W	30 mg/Kg	20 mg/Kg	15 mg/Kg

During Cycle 1 (C1) only, magrolimab will be administered on D1 and cetuximab and pembrolizumab (Cohort A) or cetuximab and docetaxel (Cohort B) will be administered on D2. During C1 days 8 and 15 and from cycle 2 on, all three drugs in both cohorts can be administered the same day.

In both arms, magrolimab and cetuximab Q2W can be used during maintenance (cetuximab 500 mg/m^2 and magrolimab 30 mg/Kg) based on emerging data from ongoing trials (18, 19). If a Q2W schedule is entertained, pembrolizumab can be administered at 400 mg Q6W in Cohort A after at least 2 cycles or 6 weeks of weekly treatment. Treatment in both arms will be continued until disease progression, unacceptable side effects, or after 2 years (~104 weeks).

Cohort A: Maintenance Period Assessment

Procedures	**Maintenance Period (6-week cycle)**												
Cycle	**3**						**4+**						
Day	**D1 (±1d)**	**D8 (±1d)**	**D15 (±1d)**	**D22 (±1d)**	**D29 (±1d)**	**D36 (±1d)**	**D1 (±1d)**	**D8 (±1d)**	**D15 (±1d)**	**D22 (±1d)**	**D29 (±1d)**	**D36 (±1d)**	**EOT[m]**
Concurrent meds	X ---------- X												

Physical exam	X						X						X
Vital signs	X		X		X		X		X		X		X
Weight	X		X		X		X		X		X		X
Pregnancy test[h]	X						X						
Perfomance Status	X						X						X
Adverse Events	X ---------- X												X
Magrolimab[a]	X		X		X		X		X		X		
Cetuximab[b]	X		X		X		X		X		X		
Pembrolizumab[c]	X						X						
CBC w/diff, chemistry	X		X		X		X		X		X		
Thyroid Function[d]	X						X						
Imaging[e]	X						X[e]						

[a] Magrolimab 30mg/kg Q2W

[b] Cetuximab 500mg/m^2 Q2W

[c] Pembrolizumab 400mg Q6W

[d] Thyroid function will consist of TSH and free T4; Thyroid function will be repeated every cycle.

[e] Imaging will be performed every 1 cycle (6 weeks) ± 1 week.

[h] Pre-menopausal female subjects of childbearing potential only. Pregnancy test should be done within 14 days of starting therapy during screening and every 6 weeks (+/- 14 days) during trial therapy

[m] EOT=End of treatment. The EOT Visit will occur with disease progression, unacceptable side effects, or after 2 years of systemic therapy at least 90 days after the last dose of study therapy for Cohort A and at least 30 days after the last dose of study therapy for Cohort B. After the EOT evaluation, information on additional oncologic treatment, time to disease progression/recurrence, sites of recurrence, additional therapies, long-term survival, and other relevant clinical data may be obtained. Patients (or their family members or designees) may be contacted by telephone or in writing or by electronic mail or during clinic visits after treatment discontinuation for collection of long-term follow-up data. Long-term follow-up clinical information may also be obtained through chart reviews.

Cohort B: Maintenance Period Assessment

Procedures	**Maintenance Period (6-week Cycle)**												
Cycle	**5**						**6+**						
Day	**D1 (±1d)**	**D8 (±1d)**	**D15 (±1d)**	**D22 (±1d)**	**D29 (±1d)**	**D36 (±1d)**	**D1 (±1d)**	**D8 (±1d)**	**D15 (±1d)**	**D22 (±1d)**	**D29 (±1d)**	**D36 (±1d)**	**EOT[m]**
Concurrent meds	X ---------- X												
Physical exam	X						X						X
Vital signs	X		X		X		X		X		X		X
Weight	X		X		X		X		X		X		X
Pregnancy test[h]	X						X						
Perfomance Status	X						X						X
Adverse Events	X ---------- X												X
Magrolimab[a]	X		X		X		X		X		X		
Cetuximab[b]	X		X		X		X		X		X		

CBC w/diff, chemistry	X		X		X		X		X		X		
Thyroid Function[d]	X						X						
Imaging[e]	X						X[e]						

[a] Magrolimab 30mg/kg Q2W

[b] Cetuximab 500mg/m2 Q2W

[c] Thyroid function will consist of TSH and free T4; Thyroid function will be repeated every cycle.

[d] Imaging will be performed every 1 cycle (6 weeks) ± 1 week.

[h] Pre-menopausal female subjects of childbearing potential only. Pregnancy test should be done within 14 days of starting therapy during screening and every 6 weeks (+/- 14 days) during trial therapy

[m] EOT=End of treatment. The EOT Visit will occur with disease progression, unacceptable side effects, or after 2 years of systemic therapy at least 90 days after the last dose of study therapy for Cohort A and at least 30 days after the last dose of study therapy for Cohort B. After the EOT evaluation, information on additional oncologic treatment, time to disease progression/recurrence, sites of recurrence, additional therapies, long-term survival, and other relevant clinical data may be obtained. Patients (or their family members or designees) may be contacted by telephone or in writing or by electronic mail or during clinic visits after treatment discontinuation for collection of long-term follow-up data. Long-term follow-up clinical information may also be obtained through chart reviews.

Imaging will be performed at baseline and every 6 weeks (± 1 week). Tumor and blood for correlative studies will be collected at baseline and prior to cycle 3 day 1 (C3D1). Additional blood samples will be collected on C2D1, and at the time of progression. A tumor biopsy will be strongly encouraged but optional at progression.

4 STUDY POPULATION

4.1 Number of Patients and Patient Selection

The target population for this study are patients with R/M HNSCC. Up to 61 patients may be enrolled in the study, with up to 31 patients in Cohort A and up to 30 patients in Cohort B. The maximum sample size includes both the safety run-in part and the Phase II part of the study if a DLT is observed in both cohorts. If no DLT is observed during the safety run-in part in neither cohort, the maximum number of efficacy evaluable patients enrolled will be 49 (25 in Cohort A and 24 in Cohort B).

4.2 Inclusion Criteria

<u>All Patients</u>

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

1) Patient must have a diagnosis of recurrent or metastatic oropharynx, oral cavity, hypopharynx, or larynx squamous cell carcinoma (HNSCC), not amenable to curative-intent local therapy with known PD-L1 CPS determined by an FDA-approved test.

2) Patient has provided informed consent.

3) Patient is willing and able to comply with clinic visits and procedures outlined in the study protocol.

4) Male or female ≥ 18 years of age

5) ECOG performance status of 0 or 1

6) Laboratory measurements, blood counts:

a. Hemoglobin ≥ 9 g/dL within 24 hours prior to initial dose of study treatment. Red blood cell transfusions are permitted to meet the hemoglobin inclusion criteria, within limits set per exclusion criterion 6.

b. Absolute neutrophil count ≥ 1.2 x 10^9/mL

c. Platelets ≥ 100 x 109/mL

7) Laboratory measurements, renal function:

Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or if elevated, a calculated glomerular filtration rate > 40 mL/min/1.73m^2 per CKD-EPI equation.

8) Laboratory measurements, hepatic function:

a. AST and ALT ≤ 2.5 x ULN or ≤ 5 x ULN in patients with liver metastases

b. Total bilirubin ≤ 1.5 x ULN or ≤ 3.0 x ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or genetic equivalent

9) Laboratory measurements, coagulation function:

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

10) Female patients with reproductive potential must practice two effective contraceptive measures for the duration of study drug therapy and for at least 6 months after completion of study therapy. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. The following are considered adequate barrier methods of contraception: diaphragm, condom, copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

11) Male patients who are sexually active with women with reproductive potential must agree to use contraception for the duration of treatment and for at least 6 months after completion of study therapy.

12) Measurable disease according to RECIST, version 1.1

13) 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.

14) Absence of active auto-immune disease or any other contra-indication to pembrolizumab, cetuximab, docetaxel or magrolimab

Cohort A:

In addition to meeting the inclusion criteria for all patients, patients who are enrolled into Cohort A must fulfill the following cohort-specific inclusion criteria:

15) PD-L1 CPS must be ≥ 1

16) Patients should not have had prior systemic therapy administered in the recurrent or metastatic setting. Systemic therapy that was completed more than 3 months prior to signing consent if given as part of multimodal treatment for locally advanced disease is allowed.

Cohort B:

In addition to meeting the inclusion criteria for all patients, patients who are enrolled into Cohort B must fulfill the following cohort-specific inclusion criterion:

17) Patients must have received at least 1 and no more than 2 lines of prior systemic anticancer therapy in the recurrent/metastatic setting not including docetaxel but including anti-PD1. Patients must have progressed on anti-PD1 (radiographically or clinically) or developed intolerable adverse events attributed to anti-PD1 that lead to treatment discontinuation and eventual disease progression.

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
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, 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) 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)
4) Red blood cell transfusion dependence, defined as requiring more than 2 units of packed RBC transfusions during the 4-week period prior to screening. Red blood cell transfusions

are permitted during the screening period and prior to enrollment to meet the hemoglobin inclusion criterion.

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

6) Known inherited or acquired bleeding disorders

7) Prior treatment with CD47 or SIRPα-targeting agents

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

9) 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

10) 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 biopsy, 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.

11) 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.

12) Prior allogeneic tissue/solid organ transplant

13) Current participation in another interventional clinical study

14) History of previous malignancy other than malignancy treated with curative intent and with no evidence of active disease ≥ 2 years before the first dose of the study drugs and of low potential risk for recurrence. Patients with the following diagnoses represents an exception and may enroll:

    a. Non-melanoma skin cancers with no current evidence of disease
    b. Melanoma in situ with no current evidence of disease
    c. Localized cancer of the prostate with prostate-specific antigen of <1 ng/mL
    d. Treated or localized well-differentiated thyroid cancer
    e. Treated cervical carcinoma in situ
    f. Treated ductal/lobular carcinoma in situ of the breast

15) Evidence of uncontrolled, active infection, requiring systemic anti-bacterial, anti-viral or anti-fungal therapy ≤ 10 days prior to administration of investigational product. Patients with known hepatitis B, hepatitis C (HCV), or HIV infection could go on study provided the viral load is undetectable at Screening.

16) 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

17) Female subjects who are pregnant or breast-feeding

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

4.4 Screen Failures

Participants who are consented to participate in the clinical trial, who do not meet one or more criteria required for participation in the trial during the screening procedures, are considered screen failures.

4.5 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

5 TREATMENT PLAN

Investigational medicinal product (IMP) is defined as magrolimab + cetuximab + pembrolizumab combination in cohort A, and magrolimab + cetuximab + docetaxel in cohort B. Details of each IMP component to be administered are shown in Table 5.

Table 5

Intervention name	**Magrolimab**	**Pembrolizumab**[b]
Type	Biologic	Biologic
Dose formulation	Concentrate for solution for infusion	Concentrate for solution for infusion
Unit dose strength(s)	20 mg/mL	25 mg/mL
Dosage level(s) [a]	1 mg/kg priming dose 30 mg/Kg every week	200 mg every 3 weeks
Route of administration	IV infusion over 3 hours (first infusion); and over 2 hours for subsequent infusions. Prior to administration of drugs.	IV infusion over 30 minutes through an IV line containing a sterile 0.2 micron to 5 micron in-line or add-on filter
Packaging and labeling	Supplied in a single-dose vial in a treatment box. Each vial contains 20 mg/mL and has an extractable volume of 10 mL. Each vial and treatment box will be labeled as required per country requirement.	Supplied in a single-dose vial in a treatment box. Each vial contains 100 mg/4 mL (4 mL). Each vial and treatment box will be labeled as required per country requirement.
Current names or aliases	Not applicable	Keytruda®
Intervention name	**Cetuximab**[b]	**Docetaxel**[b]
Type	Biologic	Cytotoxic anticancer drug
Dose formulation	Concentrate for solution for infusion	Concentrate for solution for infusion

Unit dose strength(s)	20 mg/mL	20 mg/mL
Dosage level(s)[a]	400 mg/m^2 loading dose 250 mg/m^2 weekly	30 mg/m^2 weekly
Route of administration	IV infusion over 120-min (loading dose); and over 60-min for subsequent infusions.	IV infusion over 60 minutes through an IV line containing a sterile 0.2 micron to 5 micron in-line or add-on filter
Packaging and labeling	100 mg/50 mL, single-use vial OR 200 mg/100 mL, single-use vial.	Single use vials 20 mg/mL, 80 mg/4 mL, or 160 mg/8 mL
Current names or aliases	Erbitux®	Taxotere®

[a] The total dose will be calculated based on the weight on the day of the infusion or the most recent weight assuming it was assessed in a reasonable time frame according to Investigator assessment. [b], Pembrolizumab, cetuximab, and docetaxel are commercially sourced. Information regarding their formulation can be found in the current country-specific prescribing information.

5.1 Agent Administration

5.1.1 Magrolimab

5.1.1.1 Packaging and Labeling

Formulation: magrolimab is provided as a 20 mg/mL concentrate for solution for infusion in a single-dose vial with an extractable volume of 10 mL. For magrolimab preparation, handling, and storage, refer to Appendix D.

Route of administration: intravenous (IV) infusion.

Dose regimen: First magrolimab (priming) infusion will be 3 hours (±30 min) with dose of 1 mg/kg. For the subsequent doses, the magrolimab infusion will be 2 hours (±30 min) with dose of 30 mg/kg. 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 Premedication: oral acetaminophen 650 to 1000 mg and oral or IV diphenhydramine 25 to 50 mg or comparable regimen. If less than 4 hours has elapsed since a prior dose of acetaminophen has been given, the dose of acetaminophen premedication may be omitted. 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.

When magrolimab is given in combination with cetuximab, pembrolizumab, and/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. Post infusion monitoring should begin after the infusion is complete but prior to administering any other study drug. Post infusion 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.

Patients may continue study treatment until they show evidence of disease progression, relapse, loss of clinical benefit, or unacceptable toxicity.

5.1.1.2 Magrolimab: Dose Modifications and Delays

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 adverse event, 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 ≤2 or baseline. Depending on the duration of the dose hold, repriming may be required as outlined in Table 6 below. If the investigator feels deviation from the above is needed, the PI should be consulted. Guidance on the management of anemia, infusion reactions and late hypersensitivity reactions, and pneumonitis are available in the Appendix.

Criteria for permanent discontinuation of magrolimab include the following:

- Grade 4 IRR
- Grade 4 non-hematologic 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.

The repriming guidelines shown in Table 6 should be followed for patients with dose delays. Magrolimab dosing and safety assessments should follow Cycle 1 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 usual scheduling.

Table 6. 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
30mg/kg	Weekly	4 weeks
	Every 2 weeks	4 weeks

5.1.1.3 Magrolimab Dosing Guidance for Planned Surgical Procedures on Study

If planned surgical procedures are needed for patients on study treatment, magrolimab will be delayed and restarted in accordance with table 7.

Table 7. Magrolimab Dosing Guidance for Surgical Procedure

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

5.1.2 Cetuximab

5.1.2.1 Packaging and Labeling

Formulation: cetuximab is commercially sourced. Information regarding the formulation can be found in the current country-specific prescribing information. Cetuximab preparation, handling, and storage will be performed according to the approved label.

Route of administration: intravenous (IV) infusion.

Dose regimen: Cetuximab loading dose (400mg/m^2) will be administered over 2 hours (± 10 min). Subsequent weekly cetuximab doses (250mg/m^2) will be administered over 1 hour (± 10 min). Cetuximab 500 mg/m2 maintenance dose will be administered over 2 hours (± 10 min) .

Patients may continue study treatment until they show evidence of disease progression, relapse, loss of clinical benefit, or unacceptable toxicity.

5.1.2.2 Cetuximab: Dose Modifications and Delays

Cetuximab is known to cause infusion reactions, dermatologic toxicities, and pulmonary toxicities. Dose reductions per key toxicities are described below (Table 8) and are in accordance with the cetuximab prescribing information.

Table 8 Cetuximab Dose Modification and Toxicity Management Guidelines

Adverse Reaction	Severity (CTCAE v5.0)	Dose Modification
Infusion Reaction	Grade 1 or 2	Reduce the infusion rate by 50%.
	Grade 3 or 4	Immediately and permanently, discontinue cetuximab.
Dermatologic toxicities and infectious sequelae (e.g., acneiform rash, mucocutaneous disease)	1st occurrence; Grade 3 or 4	Delay infusion 1 to 2 weeks; if condition improves, continue at 250 mg/m^2. If no improvement, discontinue cetuximab.
	2nd occurrence; Grade 3 or	Delay infusion 1 to 2 weeks; if condition improves,

	4	continue at 200 mg/m^2. If no improvement, discontinue cetuximab.
	3rd occurrence; Grade 3 or 4	Delay infusion 1 to 2 weeks; if condition improves, continue at 150 mg/m^2. If no improvement, discontinue cetuximab.
	4th occurrence; Grade 3 or 4	Discontinue cetuximab.
Pulmonary toxicity	Acute onset or worsening pulmonary symptoms	Delay infusion 1 to 2 weeks; if condition improves, continue at the dose that was being administered at the time of occurrence. If no improvement in 2 weeks or interstitial lung disease (ILD) is confirmed, discontinue ERBITUX.

5.1.3 Pembrolizumab

5.1.3.1 Packaging and Labeling

Formulation: pembrolizumab is commercially sourced. Information regarding the formulation can be found in the current country-specific prescribing information. Pembrolizumab preparation, handling, and storage will be performed according to the approved label.

Route of administration: intravenous (IV) infusion.

Dose regimen: Pembrolizumab will be administered at a dose of 200 mg using a 30-minute (±10 minutes) IV infusion.

Patients may continue study treatment until they show evidence of disease progression, relapse, loss of clinical benefit, or unacceptable toxicity.

5.1.3.2 Pembrolizumab: Dose Modifications and Delays

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

Table 9 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

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.

5.1.4 Docetaxel

5.1.4.1 Packaging and Labeling

Formulation: Docetaxel is commercially sourced. Information regarding the formulation can be found in the current country-specific prescribing information. Docetaxel preparation, handling, and storage will be performed according to the approved label.

Route of administration: intravenous (IV) infusion.

Dose regimen: docetaxel will be administered at a dose of 30mg/m^2 using a 1 hour (±10 minutes) IV infusion, every week, for 2 – 4 cycles (1 cycle = 21 days).

Premedication and Prophylaxis: For docetaxel treatment, patients can be premedicated with oral corticosteroids such as dexamethasone 4 mg twice daily for 3 days starting 1 day prior to docetaxel administration to reduce the incidence and severity of fluid retention and the severity of hypersensitivity reactions.

5.1.4.2 Docetaxel: Dose Modifications

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. Of note, coadministration of a strong CYP3A4 inhibitor should be avoided; docetaxel dose should be reduced by 50% if a strong CYP3A4 inhibitors cannot be avoided.

a. Neutropenia

Docetaxel causes neutropenia; guidance on dose reductions is shown in Table 10. Patients should have an absolute neutrophil count ≥ 1500 cells/μL before initiating the next cycle of docetaxel therapy. Myeloid growth factor support is allowed per institutional guidelines

Table 10: Docetaxel Dose Modification Guidelines for Neutropenia

Hematologic Toxicity	Occurrence	Weekly Docetaxel Dose (mg/m^2)
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	25
	Second	20
	Third	Discontinue treatment

ANC = absolute neutrophil count

b. Hepatic Toxicity

Docetaxel may be withheld for Grade 3 or 4 hepatic toxicity deemed related to docetaxel as specified in Table 11. 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 11: Docetaxel Dose Modification Guidelines for Hepatic Toxicity

Hepatic Toxicity	Occurrence	Docetaxel Dose Modification

AST or ALT > 1.5 x ULN (or baseline if higher) and alkaline phosphatase > 2.5 x ULN or Bilirubin > 1.25 x ULN	First	Interrupt treatment until AST/ALT ≤ 1.5 x ULN and alkaline phosphatase ≤ 2.5 x ULN, then reduce to 25 mg/m^2 Interrupt treatment until bilirubin ≤ 1.25 x ULN, then reduce to 25 mg/m^2 If toxicity does not resolve to above criteria within 3 weeks, discontinue treatment
	Second	Interrupt treatment until AST/ALT ≤ 1.5 x ULN and alkaline phosphatase ≤ 2.5 x ULN, then reduce to 20 mg/m^2 Interrupt treatment until bilirubin ≤ 1.25 x ULN, then reduce to 20 mg/m^2 If toxicity does not resolve to above criteria within 3 weeks, discontinue treatment
	Third	Discontinue treatment
AST or ALT > 3 x ULN (or baseline if higher) and Bilirubin > 2 x ULN	Any	Discontinue treatment
Bilirubin > 5 x ULN	Any	Discontinue treatment
AST or ALT > 5 to 10 x ULN for > 2 weeks or AST or ALT > 10 x ULN or baseline	Any	Discontinue treatment

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

c. Peripheral Neuropathy

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

d. Other Toxicities

Docetaxel dose modifications for other Grade 3 or 4 hematologic or nonhematologic toxicities deemed related to docetaxel are shown in Table 12. Docetaxel should be delayed until improvement of the Grade 3 or 4 toxicity to at least Grade 2 or baseline.

Table 12: Docetaxel other toxicities management

Other Toxicity	Occurrence	Weekly Docetaxel Dose (mg/m^2)
Grade 3 or 4 nonhematologic or hematologic toxicity[a] that does not resolve to ≤ Grade 2 within 14 days	First	Delay 25
	Second	20
	Third	Discontinue treatment

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

5.2 Preparation/Handling/Storage/Accountability

Docetaxel, Cetuximab and Pembrolizumab are commercially sourced. Their preparation, handling, and storage will be performed according to the approved label. The IMP magrolimab will be supplied for the study by Gilead. Preparation and administration of magrolimab are detailed in the pharmacy manual. Magrolimab will be shipped to MD Anderson Cancer Center (MDACC) with a Drug Shipment and Proof of Receipt form. A drug accountability log will be maintained. The information contained on the log should be sufficient to comply with applicable good clinical practice (GCP) regulations. At the time of study closure, both the unused, used, and expired study drug will be destroyed by MD Anderson's Investigational Pharmacy Services per MD Anderson's institutional standard operating procedure (SOP).

5.3 IND Agent(S)/IDE Device(s)

Please refer to Section 5.1 "Agent Administration".

5.4 Other Modality(ties) or Procedures

N/A

5.5 Dose Expansion Cohorts

N/A

5.6 General Concomitant Medication and Supportive Care Guidelines

5.6.1 Allowed Medications

All treatments that the investigator considers necessary for the subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. A single dexamethasone dose of up to 12 mg can be administered prior to exam under anesthesia/biopsy as per investigator discretion. A brief course of systemic glucocorticoids (≤7 days) is also allowed for contrast-dye allergy.

All concomitant medications received within 28 days before the first dose of trial treatment through the EOT visit will be recorded in the electronic medical record (EMR).

5.6.2 Prohibited Concomitant Medication

The subject is prohibited from receiving the following therapies during the Screening and Treatment periods of this study:

- Exposure to any investigational drug within 4 weeks or 5 half-lives whichever is longer or concurrently with IP administration.
- Chronic immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and

TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted.

- Live attenuated vaccines within 30 days of IMP dosing (i.e., 30 days prior to the first dose). Inactivated vaccines, such as the injectable influenza vaccine, are permitted.
- Coadministration of docetaxel and a strong CYP3A4 inhibitor should be avoided; if a strong CYP3A4 inhibitors cannot be avoided, docetaxel dose should be reduced by 50% as stated in section 5.1.4.2

5.7 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 2 years (~104 weeks) or until one of the following criteria applies:

- Disease progression by RECIST v1.1
- 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 progression of disease (PD) is considered a sufficient reason for discontinuing a patient from study treatment, given that delayed treatment benefit can be seen with immunotherapies, the investigator is allowed to continue to treat the patient beyond progression until confirmation of disease progression through a subsequent assessment at least 4 weeks apart (ie, disease worsening compared to the previous assessment) with the option of continuing treatment while awaiting radiologic confirmation of PD. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar. If repeat imaging confirms PD, subjects will be discontinued from study therapy. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions. The decision to continue study treatment after the first evidence of PD is at the Investigator's discretion based on the clinical status of the subject. Subjects may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG PS
- Absence of rapid progression of disease

- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Patients discontinued from treatment should still comply with the End of Study visit.

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.8 Duration of Follow-up

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

5.9 Dosing Delays/Dose Modifications

Please refer to Section 5.1 “Agent Administration”.

6 STUDY ASSESSMENTS AND PROCEDURES

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

The investigator must document any deviation from the protocol procedures and notify the IRB and the sponsor.

6.1 Schedule of Activities (SoA)

6.1.1 COHORT A: Anti-PD1 naïve, treatment with magrolimab, cetuximab and pembrolizumab

Table 1. Study Assessment Cohort A

Procedures[a]	**Screening**	**Cycle (21-Day Cycles)**													
		1				**2**			**3**			**(…) 34**			
Cycle Day (Visit window)	**Days -28 to -1**	**D1**	**D2**	**D8 (±2d)**	**D15 (±2d)**	**D1 (±2d)**	**D8 (±2d)**	**D15 (±2d)**	**D1 (±2d)**	**D8 (±2d)**	**D15 (±2d)**	**D1 (±2d)**	**D8 (±2d)**	**D15 (±2d)**	**EOT**[m]
Informed consent	X														
Demographics	X														
Medical history	X														
Elegibility Verification	X														
Concurrent meds		X ---------- X													
Physical exam[b]	X	X				X			X			X			X
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X				X			X			X			X
Height	X														
Performance Status	X	X				X			X			X			X
Tumor sample[d]	X														
Adverse Events		X ---------- X													X
Magrolimab		X		X	X	X	X	X	X	X	X	X	X	X	
Cetuximab						X	X	X	X	X	X	X	X	X	
Pembrolizumab[e]			X			X			X			X			
CBC w/diff, chemistry[f]	X	X				X			X			X			X
Blood Type and Cross Match	X														
Coagulation parameters[g]	X														
Serum pregnancy test[h]	X								X						
Thyroid function[i]	X								X						X
EKG[j]	X														
Imaging[k]	X								X						
Hb/Ht[n]		X		X											
Blood for biomarkers[l]		X				X			X						
Viral Panel[o]	X														

a All procedures (X) to be performed pre-infusion unless stated otherwise.
b Full physical examination at baseline; targeted physical examination at other time points.
c Vital signs include temperature, blood pressure, pulse, and respiratory rate.
d Baseline tumor biopsy is mandatory with two exceptions: 1) the patient recently underwent tumor biopsy and have a minimum of 1 block and/or 20 unstained slides available for future correlative analysis; in this case, the tumor biopsy is strongly encouraged but not mandatory; 2) the patient underwent a tumor biopsy prior to signing consent and

adequate tissue was banked by another MDACC tissue collection protocol (Eg: lab02-039) and the tissue can be transferred for use in this protocol; in this case, a biopsy can be waived. Additionally, a tumor biopsy will be strongly encouraged but optional at progression.

e Pembrolizumab can be administered at 400 mg Q6W, if a Q2W schedule is entertained for magrolimab and cetuximab.

f CBC w/diff include CBC with hemoglobin, WBC with differential, and platelet count. Chemistry include sodium, potassium, chloride, magnesium, glucose, creatinine, blood urea nitrogen (BUN), ALT, AST, total bilirubin, and alkaline phosphatase (ALP). CBC needs to be completed within 24 hours prior to C1D1, chemistry can be done within 7 days of C1D1.

g Coagulation tests: prothrombin time, PTT and INR performed at Screening and as clinically indicated.

h Pre-menopausal female subjects of childbearing potential only. Pregnancy test should be done within 14 days of starting therapy during screening and every 6 weeks (+/- 14 days) during trial therapy

i Thyroid function will consist of TSH and free T4; Thyroid function will be repeated every 2 cycles.

j Electrocardiogram during screening, thereafter as clinically indicated.

k Imaging will be performed at baseline and every 6 weeks ± 1 week.

l Blood for correlative studies will be collected at baseline and prior to cycle 3 day 1 (C3D1). Additional blood samples will be collected on C2D1, and at the time of progression. The following samples will be collected for future biomarker analysis: EDTA Vacutainer® (checkpoint markers/CAFs): 10 mL = 1 x 10 mL; Streck Cell Free-DNA BCT (ctDNA): 20 mL = 2x 10 mL; and Sodium Heparin (immunoprofiling): 40 ml = 4 x 10 mL. Missed research blood collection will not constitute a protocol violation.

m EOT=End of treatment. The EOT Visit will occur with disease progression, unacceptable side effects, or after 2 years of systemic therapy at least 90 days after the last dose of study therapy for Cohort A and at least 30 days after the last dose of study therapy for Cohort B. After the EOT evaluation, information on additional oncologic treatment, time to disease progression/recurrence, sites of recurrence, additional therapies, long-term survival, and other relevant clinical data may be obtained. Patients (or their family members or designees) may be contacted by telephone or in writing or by electronic mail or during clinic visits after treatment discontinuation for collection of long-term follow-up data. Long-term follow-up clinical information may also be obtained through chart reviews.

n Hb and hematocrit must be checked 3 to 6 hours after the initiation of the first and second doses of magrolimab

o HIV, hepatitis B and/or hepatitis C viral load will be required at Screening only for patients with known history of HIV, hepatitis B, and/or hepatitis C

6.1.2 COHORT B: Anti-PD1 refractory, treatment with magrolimab, cetuximab and docetaxel

Table 2: Study Assessment Cohort B

Procedures[a]	**Screening**	**Cycle (21-Day Cycles)**													
Cycle		**1**				**2**			**3**			**(…) 34**			
Cycle Day (Visit window)	**Days -28 to -1**	**D1**	**D2**	**D8 (±2d)**	**D15 (±2d)**	**D1 (±2d)**	**D8 (±2d)**	**D15 (±2d)**	**D1 (±2d)**	**D8 (±2d)**	**D15 (±2d)**	**D1 (±2d)**	**D8 (±2d)**	**D15 (±2d)**	**EOT**[m]
Informed consent	X														
Demographics	X														
Medical history	X														
Elegibility Verification	X														
Concurrent meds		X ---------- X													
Physical exam[b]	X	X				X			X			X			X
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X				X			X			X			X
Height	X														
Perfomance Status	X	X				X			X			X			X
Tumor sample[d]	X														
Adverse Events		X ---------- X													X
Magrolimab		X		X	X	X	X	X	X	X	X	X	X	X	
Cetuximab			X	X	X	X	X	X	X	X	X	X	X	X	
Docetaxel[e]						X	X	X	X	X	X				
CBC w/diff, chemistry[f]	X	X				X			X			X			X
Blood Type and Cross Match	X														
Coagulation parameters[g]	X														
Serum pregnancy test[h]	X								X						
Thyroid function[i]	X								X						X
EKG[j]	X														
Imaging[k]	X								X						
Hb/Ht[n]		X		X											
Blood for biomarkers[l]		X				X			X						

a All procedures (X) to be performed pre-infusion unless stated otherwise.
b Full physical examination at baseline; targeted physical examination at other time points.
c Vital signs include temperature, blood pressure, pulse, and respiratory rate.
d Baseline tumor biopsy is mandatory with two exceptions: 1) the patient recently underwent tumor biopsy and have a minimum of 1 block and/or 20 unstained slides available for future correlative analysis; in this case, the tumor biopsy is strongly encouraged but not mandatory; 2) the patient underwent a tumor biopsy prior to signing consent and adequate tissue was banked by another MDACC tissue collection protocol (Eg: lab02-039) and the tissue can be transferred for use in this protocol; in this case, a biopsy can be waived. Additionally, a tumor biopsy will be strongly encouraged but optional at progression.

e Docetaxel will be administered only for 2 to 4 cycles.
f CBC w/diff include CBC with hemoglobin, WBC with differential, and platelet count. Chemistry include sodium, potassium, chloride, magnesium, glucose, creatinine, blood urea nitrogen (BUN), ALT, AST, total bilirubin, and alkaline phosphatase (ALP). CBC needs to be completed within 24 hours prior to C1D1, chemistry can be done within 7 days of C1D1.
g Coagulation tests: prothrombin time, PTT and INR performed at Screening and as clinically indicated.
h Pre-menopausal female subjects of childbearing potential only. Pregnancy test should be done within 14 days of starting therapy during screening and every 6 weeks (+/- 14 days) during trial therapy
i Thyroid function will consist of TSH and free T4; Thyroid function will be repeated every 2 cycles.
j Electrocardiogram during screening, thereafter as clinically indicated.
k Imaging will be performed at baseline and every 6 weeks ± 1 week.
l Blood for correlative studies will be collected at baseline and prior to cycle 3 day 1 (C3D1). Additional blood samples will be collected on C2D1, and at the time of progression. The following samples will be collected for future biomarker analysis: EDTA Vacutainer® (checkpoint markers/CAFs): 10 mL = 1 x 10 mL; Streck Cell Free-DNA BCT (ctDNA): 20 mL = 2x 10 mL; and Sodium Heparin (immunoprofiling): 40 ml = 4 x 10 mL. Missed research blood collection will not constitute a protocol violation.
m EOT=End of treatment. The EOT Visit will occur with disease progression, unacceptable side effects, or after 2 years of systemic therapy at least 90 days after the last dose of study therapy for Cohort A and at least 30 days after the last dose of study therapy for Cohort B. After the EOT evaluation, information on additional oncologic treatment, time to disease progression/recurrence, sites of recurrence, additional therapies, long-term survival, and other relevant clinical data may be obtained. Patients (or their family members or designees) may be contacted by telephone or in writing or by electronic mail or during clinic visits after treatment discontinuation for collection of long-term follow-up data. Long-term follow-up clinical information may also be obtained through chart reviews.
n Hb and hematocrit must be checked 3 to 6 hours after the initiation of the first and second doses of magrolimab

6.2 Screening phase

All subjects must first read, understand, and sign the institutional review board approved informed consent before any study-specific screening procedures are performed. After signing the informed consent, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study using the institutional database (CORe). Procedures that are performed prior to the signing of the informed consent and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window. That includes screening physical examination, hematology, blood chemistry and radiologic imaging. A biopsy will be mandatory during Screening, unless 1) the patient recently underwent tumor biopsy and have a minimum of 1 block and/or 20 unstained slides available for future correlative analysis; in this case, the tumor biopsy is strongly encouraged but not mandatory; 2) the patient underwent a tumor biopsy prior to signing consent and adequate tissue was banked by another MDACC tissue collection protocol and the tissue can be transferred for use in this protocol; in this case, a biopsy can be waived. Tumor PD-L1 CPS must be documented in the EMR. Tissue will be banked for biomarker analysis.

6.3 Adverse Events

At each visit, all AEs observed by the investigator or reported by the patient that occur from the first day of administration of the investigational agent (C1D1) through 30 days after the last dose of study treatment are to be reported using the applicable electronic case report form (eCRF). Full details on the definitions, assessment, and reporting instructions for AEs are provided in Section 10.

6.4 Biomarker Assessments

Biospecimen samples will be collected to assess treatment response biomarkers and to define correlates of clinical efficacy and/or safety, as outlined in Section 2.3. The biomarker sample collection schedules are outlined in Table 1 and Table 2.

Patients are required to submit mandatory pretreatment tumor tissue from a core needle or excisional tumor biopsy (fine needle aspirate is not adequate). A newly obtained biopsy collected within 90 days prior to study treatment start is strongly preferred, but an archival sample is acceptable.

The correlative analysis includes but are not limited to efficacy according to baseline tumor PD-L1 CPS and mutational profile.

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

6.5 Biospecimen repository

As part of the study, a tissue and blood sample repository will be created. The objective of this biospecimen sample repository will be to provide material for future evaluations of other relevant biomarkers that may be associated with clinical outcomes. Some of the de-identified tissue, blood, and oral rinse samples might be transferred to outside vendors for biomarker analysis. A written informed consent will be obtained from patients enrolled in this study so that these remaining samples may be analyzed in the future for biomarkers. Samples will be banked at MDACC. If a subject withdraws consent to the use of donated samples, the samples will be disposed of/destroyed, and the action documented.

6.6 Safety Assessments

Safety will be assessed at every clinical visit and in an ongoing basis throughout the study from the first day of administration of the investigational agent (Cycle 1 Day 1) through 30 days after the last dose of study treatment. All patients who receive at least one dose of the investigational agent will be included in the safety analysis. Adverse events (AEs) will be graded using NCI-CTCAE version 5. Frequency of AEs, serious AEs, discontinuation of study drug due to AEs and changes from baseline laboratory parameter values will be evaluated.

6.7 End of Treatment (EOT) Visit

In order to ensure more adequate capture of immune-related adverse events, the EOT visit for an individual patient will occur at least 90 days after the last dose of study therapy for Cohort A. For Cohort B, the EOT visit will occur at least 30 days after the last dose of study therapy.

6.8 Long-term follow-up

After the End of Treatment evaluation, information on additional oncologic treatment, time to disease progression/recurrence, sites of recurrence, additional therapy for recurrence, long-term survival, and other relevant clinical data may be obtained. Patients (or their family members or designees) may be contacted by telephone or in writing or by electronic mail or during clinic visits

after treatment discontinuation for collection of long-term follow-up data. Long-term follow-up clinical information may also be obtained through chart reviews.

6.9 End of Study

For 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).
For 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.

7 ADVERSE EVENT, SERIOUS ADVERSE EVENT (SAE)

Investigators will assess the occurrence of adverse events (AE) and serious adverse events (SAE) at all subject evaluation time points during the study as per Schedule of Assessments.

Assessments will consist of monitoring and recording of AEs and serious AEs, physical examination, measurement of protocol-specific laboratory variables and vital signs, as well as other tests deemed important for this protocol. Circumstances in which these assessments should be reported as AEs are described below. AE's will be collected, graded, attribution assigned on AE logs that will be available in the EMR and entered on Case Report Form (CRF) in the DMI database. The AE duration (i.e., start and end dates) and action taken will also be recorded. Gilead will receive a copy of the investigational new drug (IND) office eSAE form. All patients who have received at least one exposure to study drug will be evaluated for safety of the study drug.

7.1 Definition of Adverse Events (AE)

An AE is defined as any untoward medical occurrence in a patient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory test result), symptom, or disease temporally associated with the use of the study treatment, whether or not it is considered to be study drug(s) related. Included in this definition are any newly occurring events and any previous condition that has increased in severity or frequency since the administration of study

All AEs that are observed by the Investigator, staff or mentioned by the subject either spontaneously or upon questioning will be recorded in the AE log and entered in the study database.

The following are **NOT** considered AEs:

- Pre-existing condition: A pre-existing condition (documented on the medical history) is not

considered an AE unless the severity, frequency, or character of the event worsens during the study period.

- Pre-planned or elective hospitalization: A planned hospitalization (Eg: surgery) is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of investigational agent, or due to long travel distances are also not SAEs.
- Diagnostic Testing and Procedures: Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.
- Any adverse event clearly attributable to disease progression

The causality of AEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and attributions will be made as per below:

- **Attribution** - the determination of whether an adverse event is related to a medical treatment or procedure.
- **Definite** - the adverse event is clearly related to the investigational agent(s).
- **Probable** - the adverse event is likely related to the investigational agent(s).
- **Possible** - the adverse event may be related to the investigational agent(s).
- **Unlikely** - the adverse event is doubtfully related to the investigational agent(s).
- **Unrelated** - the adverse event is clearly NOT related to the investigational agent(s).

The severity of the adverse events (AEs) will be graded according to the U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE), Version **5.0**.

Events not included in the NCI CTCAE will be scored as follows:

- **Grade 1:** Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.
- **Grade 2:** Moderate: discomfort present with some disruption of daily activity, require treatment.
- **Grade 3:** Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
- **Grade 4:** Life Threatening: discomfort that represents immediate risk of death
- **Grade 5:** Death

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events, assigning the attribution and assessing the severity of the AE, the causal relationship between any events and the clinical study procedure, activities or device. Additionally, the Investigator is responsible for providing appropriate treatment for the

event and for adequately following the event until resolution for all adverse events for subjects enrolled.

7.2 Adverse Event of Special Interest (AESI)

An adverse event of special interest is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment. The following events need to be reported as AESIs:

• Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP;

- Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial.
- In the event of pregnancy in a female participant, IMP should be discontinued.
- Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.

• Symptomatic overdose (serious or nonserious) with IMP/NIMP

- An overdose of IMP is defined as: increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.
- An overdose (accidental or intentional) with the NIMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.

• An elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) lab value that is greater than or equal to 3 times the ULN and an elevated total bilirubin lab value that is greater than or equal to 2 times the ULN and, at the same time, an alkaline phosphatase lab value that is less than 2 times the ULN, as determined by way of protocol specified laboratory testing or unscheduled laboratory testing*.

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor.

• Other project-specific AESIs

- infusion-related reaction Grade ≥2
- Cytokine Release Syndrome Grade ≥2
- Immune effector cell associated neurotoxicity of any grade
- Vascular leak syndrome of any grade
- Any immune-related AE Grade ≥3
- Arrhythmia Grade ≥3

7.3 Unexpected Adverse Events

An “unexpected” AE is an AE that is not listed in the Investigator's Brochure/package insert or is not listed at the specificity or severity that has been observed. "Unexpected" also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

Adverse Events or Adverse Device Effects will be captured according to protocol phase I recording guidelines:

Recommended Adverse Event Recording Guidelines					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

7.4

Serious Adverse Event (SAE) Reporting Requirements for MD Anderson Sponsored IND Protocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
  Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the applicable Institutional Review Board (IRB) of record in accordance with their timeframes and procedures.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of study drug, unless the participant withdraws consent.
- Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- All SAEs, expected or unexpected/ initial or follow up, including the development of new malignancies, must be reported to the IND Office within 5 working days of knowledge of the event regardless of the attribution.

- Death or life-threatening events that are unexpected, possibly, probably or definitely related to the study drug must be reported (initial or follow up) to the IND Office within 24 hours of knowledge of the event.

- Additionally, any serious adverse events that occur after the 30 day time period, that are related to the study treatment must be reported to the IND Office. This may include the development of new malignancies.

- The electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office.

- All events reported to the supporting company must also be reported to the IND Office.
  Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

7.3.1 Investigator Communication with Supporting Companies

The investigator and research team will inform Gilead of any SAE or AESI as assessed by the PI and will forward all IND Office eSAE reports to Gilead according to the IND Office reporting requirement timelines (Section 7.4). A cover page will accompany the form indicating:

a. Notification from an Investigator Sponsored Study
b. The Investigator IND number assigned by the FDA
c. The Investigator's name and address

If it is not possible to record and transmit the SAE information electronically, the SAE will be reported on the paper SAE reporting form and transmitted by Fax.

The reportable will be timely submitted to Gilead's Central Safety Mailbox or Fax. All events submitted to the supporting company should also be sent to the IND Sponsor.

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

7.4 Adverse Event Reporting Period

All AEs whether serious or non-serious, will be captured from the time of the first administration of the investigational agent until 30 days following the last dose of study drug or until the initiation of alternative anticancer therapy. Progressive disease should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported.

All Grade 3 – 5 adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself.

7.5 Other events requiring reporting

7.5.1 Overdose

Any overdose of IMP should be recorded in the medical records (including quantity of the excess dose and the duration of the overdose). An overdose will not be considered an SAE unless the outcome of the overdose meets seriousness criteria. If overdose occurs, symptomatic management is indicated.

In the event of an overdose, the investigator should:

1. Contact the Sponsor (IND office) within 24 hours of knowledge
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 30 days).
3. Document appropriately in the e-CRF.

7.5.2 Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 6 months after the last dose of study combination. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 3 months after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days after the last dose of study combination must be reported. Any occurrence of pregnancy must be reported per SAE reporting timelines. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. Pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing will need to be reported per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

Pregnancy report submission is to be done via eSAE application as "Other Important Medical Event".

7.5.3 Paternal Exposure

Pregnancy of the subject's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

To capture information about a pregnancy from the partner of a male subject, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome;

the male subject should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 6 months after dosing ends should be followed up and documented.

8 RESPONSE CRITERIA

8.1 Measurement of Effect

Efficacy Assessment

Either computed tomography (CT), magnetic resonance imaging, or positron emission tomography-CT (that includes a contrast-enhanced CT component) of the head, neck, chest, and abdomen will be performed at screening, every 6 weeks (± 1 week) during the study, and at the end-of-treatment visit if a response assessment has not been performed within the last 30 days. Imaging of the pelvis is optional. Scans taken as part of standard medical practice up to 28 days prior to enrolment can be used for screening as long as they meet all study requirements.

Tumor burden will be evaluated solely based on radiographic imaging per RECIST, version 1.1 (17). For radiographic evaluations, the same method of assessment and the same technique (e.g., 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.

For patients who stop study treatment in the absence of disease progression (e.g., experienced unexpected toxicity), scans should continue to be collected approximately every 6 weeks (± 1 week) until disease progression or initiation of systemic antitumor therapy other than the study treatment, whichever is earlier.

8.2 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

8.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. The response will be assessed by a radiologist collaborator and will be documented in the EMR and in the DMI database.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

8.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that

recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

8.5 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Response and progression will be evaluated in this study using the revised international criteria (RECIST version 1.1) proposed by the RECIST committee as well as the modified iRECIST guidelines. Investigators should note the different requirements for confirmatory scans as well as follow up for the two criteria.

9 STATISTICAL CONSIDERATIONS

This two-arm phase II open-label study is designed to evaluate the safety and activity of magrolimab, cetuximab and pembrolizumab administered in first-line (Cohort A) or magrolimab, cetuximab and docetaxel administered in second or third line for PD-1-refractory (Cohort B) R/M HNSCC patients. The primary outcome is the ORR per RECIST 1.1. The study will also characterize the safety profile of the triplet therapy. All patients who received at least one dose of any investigational agent will be included in the safety analysis. Only patients who have at least one re-staging radiological assessment will be included in the efficacy analysis.

9.1 Safety and Feasibility Monitoring

To ensure patient safety, both Cohorts A and B will start with a staggered phase and a safety run-in with two-predefined doses (Section 6, Table 3 and Table 4). Initially, 6 patients will be enrolled into Safety Run-in Cohort A and B to receive a starting regimen dose (dose 0). A DLT evaluation period of 2 cycles (42 days) will occur.

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 may take place for magrolimab or other IMP, according to AEs attribution and physician discretion. Dose de-escalation decisions will be made as follows:

- If no more than 2 of 6 DLT-evaluable patients experience a DLT during the DLT evaluation window (6 weeks), enrolment into phase 2 Cohorts 1 and 2 will begin at dose level 0.

- If 3 or more (> 50%) DLT-evaluable patients experience a DLT during the DLT evaluation window (6 weeks), 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 Cohorts A and B is presented in the Section 6 (Table 3).

9.2 Sample Size Determination

9.2.1 Safety Run-in Sample Size

DLTs will be assessed during the first two cycles (6 weeks). The recommended dose is defined as the highest dose level in which 6 patients have been treated with less than 3 instances of DLT. It is anticipated that 6 to 12 eligible patients are required for the safety run-in phase of this trial. The patients treated with the selected dose in the safety run-in phase will be included in the phase II evaluation.

Following assessment of the safety/tolerability of the triple combination regimen in the safety run-in cohort, the staggered drug phase may be eliminated following recommendation of the Data and Safety Monitoring Committee.

9.2.2 Sample Size for Phase II Design for Cohort A: magrolimab, cetuximab, pembrolizumab in the first-line setting

Bayesian Optimal Phase 2 (BOP2) design will be conducted after the safety run-in phase. For Cohort A, we will enroll up to 25 evaluable patients. The triplet regimen will have a target response rate (H1) of 55%. Since the expected ORR with single agent pembrolizumab is 17% and the ORR with cetuximab + pembrolizumab is 22-45%, we will consider an ORR of 30% or lower (H0) a failure and the new regimen will be rejected under this circumstance. The time to evaluate response is 6 months. Under these assumptions, Cohort A will include 12 evaluable patients in the first stage. If an objective response is observed in 3 or fewer patients, the enrollment in Cohort A will be stopped. Otherwise, an additional 13 patients will be enrolled. The regimen will be considered worthy of further study if objective responses are observed in 12 or more patients in a total of 25 patients. This design has an alpha of 0.043 and power of 0.81. The operating characteristics are given in the following table using the BOP2 web application (BOP2 V1.4.12.0), which is available at http://www.trialdesign.org.

Scenario	Response Rate	Early Stopping (%)	Claim Promising (%)	Average Sample Size
1	0.30	49.25	4.32	18.6
2	0.55	3.56	81.03	24.5

Specifically, we monitor the efficacy endpoint using the Bayesian optimal phase 2 (BOP2) design (Zhou, Lee and Yuan, 2017). Specifically, let n denote the interim sample size and N denote the maximum sample size. Let p_{eff} denote the objective response rate and define the null hypothesis $H_0: p_{eff} \leq 0.3$, under which the treatment is deemed as unacceptable. We will stop enrolling patients and claim that the treatment is unacceptable if

$$Pr(p_{eff} > 0.3|data) < \lambda\left(\frac{n}{N}\right)^{\alpha},$$

where λ=0.92 and α=0.74 are design parameters optimized to maximize power under the alternative hypothesis $H_1: p_{eff} = 0.55$, (i.e., the probability of correctly claiming that the treatment is acceptable under H_1), while controlling the type I error rate (i.e., the probability of incorrectly claiming that the treatment is acceptable under H_0) at 0.043. This optimization is performed assuming a vague prior Beta(0.3,0.7) for p_{eff}. The above decision rule leads to the following stopping boundaries and yields a statistical power of 0.810 under H_1.

9.2.3 Sample Size for Phase II Design for Cohort B: mabrolimab, cetuximab, docetaxel in patient who have progressed on first-line systemic therapy

Bayesian Optimal Phase 2 (BOP2) design will be conducted after the safety run-in phase. For Cohort B, we will include up to 24 evaluable patients. The target ORR (H1) is 45%, with an alternative hypothesis (H0) ORR of 20% (expected ORR with single agent cetuximab is 8-13%; in combination with taxane in the platinum-refractory setting, there is no prospective data; we estimate an ORR of 20% given the ORR to single agent docetaxel in this setting is 6% and cetuximab is thought to have an additive effect in combination of chemotherapy). The time to evaluate response is 6 months. Under these assumptions, Cohort B will include 14 evaluable patients in the first stage. If an objective response is observed in 3 or fewer patients, the enrollment of Cohort B will be stopped. Otherwise, an additional 10 patients will be enrolled. The regimen will be considered worthy of further study if objective responses are observed in 9 or more patients. This design has an alpha of 0.05 and power of 0.81. The operating characteristics are given in the following table using the BOP2 web application (BOP2 V1.4.12.0), which is available at http://www.trialdesign.org.

Scenario	Response Rate	Early Stopping (%)	Claim Promising (%)	Average Sample Size
1	0.20	69.82	3.44	17.0
2	0.45	6.32	81.34	23.4

Specifically, we monitor the efficacy endpoint using the Bayesian optimal phase 2 (BOP2) design (Zhou, Lee and Yuan, 2017). Specifically, let n denote the interim sample size and N denote the maximum sample size. Let p_{eff} denote the objective response rate and define the null hypothesis $H_0: p_{eff} \leq 0.2$, under which the treatment is deemed as unacceptable. We will stop enrolling patients and claim that the treatment is unacceptable if

$$Pr(p_{eff} > 0.25|data) < \lambda\left(\frac{n}{N}\right)^{\alpha},$$

where λ=0.921 and α=0.42 are design parameters optimized to maximize power under the alternative hypothesis $H_1: p_{eff} = 0.45$, (i.e., the probability of correctly claiming that the treatment is acceptable under H_1), while controlling the type I error rate (i.e., the probability of incorrectly claiming that the treatment is acceptable under H_0) at 0.05. This optimization is performed assuming a vague prior Beta(0.2,0.8) for p_{eff}. The above decision rule leads to the following stopping boundaries and yields a statistical power of 0.81 under H_1:

9.3.2: Toxicity Monitoring in Phase II

To ensure patient safety, we will continue to monitor the treatment toxicity in Cohort A and Cohort B in the phase II part of the study, respectively. For each cohort, the study accrual will be suspended if Probability($\hat{\theta} > 0.3$) ≥ 0.7 where $\hat{\theta}$ is the estimated DLT rate. The default prior distribution Beta (0.5, 0.5) for θ is used. The corresponding stopping boundaries for Cohort A with the maximum sample size of 25 are: ≥ 3/6 or ≥ 5/12 or ≥ 7/18 or ≥ 9/24 DLTs. The operating characteristics table for the design is shown below. As can be seen, the probability of early stopping is 1.8%, 46.1%, and 95.6% if the true DLT rates are 0.1, 0.3, and 0.5, respectively.

Table 13. Operating characteristics of the early toxicity stopping for Cohort A with the maximum sample size of 25.

Table OC1: Overall Summary					
Scenario	**Prob.Of.Tox**	**Prob.Early.Stop**	**Prob.Declare.Tox**	**Avg.N.Patients**	**Avg.**
1	0.1	0.0183	0.0184	24.6698	
2	0.3	0.4612	0.4833	18.3092	
3	0.5	0.9564	0.9665	9.5205	

Similarly, for Cohort B with the maximum sample size of 24, the corresponding stopping boundaries: ≥ 3/6 or ≥ 5/12 or ≥ 7/18 or ≥ 9/24 DLTs. The operating characteristics table for the design is shown below. As can be seen, the probability of early stopping is 1.8%, 49.0%, and 97.5% if the true DLT rates are 0.1, 0.3, and 0.5, respectively.

Table 14. Operating characteristics of the early toxicity stopping for Cohort B with the maximum sample size of 24.

Table OC1: Overall Summary					
Scenario	**Prob.Of.Tox**	**Prob.Early.Stop**	**Prob.Declare.Tox**	**Avg.N.Patients**	**Avg.**
1	0.1	0.0849	0.0849	22.4061	
2	0.3	0.5786	0.6006	13.8318	
3	0.5	0.9524	0.9706	6.9829	

The above calculations were performed by the Shiny apps at https://trialdesign.org/one-page-shell.html#BTOX).

9.3 Stratification Factors

N/A

9.4 Statistical Methods and Data Analysis

Standard descriptive statistics will be provided for each continuous or categorical variable by cohorts and different dose levels that include arithmetic mean, standard deviation, median, quartiles, range for continuous variables; frequency counts and proportion for categorical variables as well as the 95% confidence intervals as appropriate. Boxplots, bar plots, variation of boxplots (e.g., swarmplot, violinplot), or heatmap etc. will be generated for visualization.

9.4.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the objective response rate by RECIST v1.1. ORR is defined as the percent of patients documented to have a confirmed CR or PR. The ORR and its exact 95% confidence interval will be calculated and presented by each cohort. Participants who are not evaluable for assessing the objective response will be considered as nonevaluable.

9.4.2 Analysis of Secondary and Exploratory Endpoints

N/A

The Investigator is responsible for completing toxicity/efficacy summary reports and submitting them to the IND Sponsor.

Run-In Phase:

After the first 6 evaluable patients, per cohort, complete 2 cycles (42 days) of DLT evaluation period and then for every 6 evaluable patients, per cohort complete 2 cycles of treatment. IND Sponsor approval must be obtained prior to expanding/changing dose levels.

Phase II:
Toxicity summary:

After the first 6 evaluable patients, per cohort, complete 2 cycles (42 days) of treatment and then for every 6 evaluable patients, per cohort complete 2 cycles of treatment.

Efficacy summary:

Cohort A

After the first 12 evaluable patients, complete 6 months of treatment in the first stage. Then after all 25 evaluable patients complete 6 months of treatment.

Cohort B

After the first 14 evaluable patients complete 6 months of treatment in the first stage. Then after the all 24 evaluable patients, complete 6 months of treatment.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

Duration of response, PFS, and OS will be analyzed using the standard Kaplan-Meier method. Median survival time with its 95% CI and KM plots will be also provided. To identify biomarkers (Blood samples and tumor tissue samples) associated with response to the treatment, Chi-squared/ Fisher's exact tests, ANOVA and the Mann-Whitney U test will be used as appropriate. Logistic regression may be utilized to assess associations between biomarkers and response adjusting by baseline covariates.

10 STUDY OVERSIGHT AND DATA REPORTING REQUIREMENTS

This protocol is monitored at several levels, as described elsewhere in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician always have access to the data.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via the mechanism described elsewhere in this section. All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

10.1 Data and Safety Monitoring Committees

MD Anderson's Data and Safety Monitoring Committees are responsible for monitoring all investigator-initiated Pilot, Phase I, I/II, II single arm, as well as randomized Phase II or higher clinical trials. This trial will adhere to institutional data safety monitoring plans.

10.2 Clinical Trial Monitoring

Regular monitoring of trial conduct will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

10.3 Study Records Retention

Essential/Source Documents may be maintained in electronic or via paper records. Electronic records must be maintained on an MD Anderson secured server accessed only by authorized research staff. Paper records must be maintained in a lockable room or cabinet accessed only by authorized research staff and must be made available in the event of an audit/inspection.

Plan for continued storage of Essential/Source Documents consistent with protocol requirements, applicable regulations, Clinical Research contracts, and the Retention of Official Medical Records Policy (MD Institutional Policy ADM0386) will be followed.

10.4 Consent Process and Documentation

We will the Office of Clinical Research SOP 04: Informed Consent Process.

11 DATA MANAGEMENT AND SHARING PLAN

11.1 Data Type

Electronic case report forms will be used for this study, stored under the Data Management Initiative (DMI) database developed by the Department of Biostatistics.

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 include investigators' Study Files and original patient clinical source documents generated at the study site.

The investigator will ensure the Study Files are maintained, including the CRFs and query forms, protocol/amendments, IRB and regulatory approvals with associated correspondence, informed consents, study drug records, staff curriculum vitae, all correspondence, and other appropriate documents.

Patient clinical source documents may include, but are not limited to, patient hospital/clinic records, physicians' and nurses' notes, appointment books, laboratory reports, ECGs, radiographs, pathology and special assessment reports. The investigator must assure that all original source documents are available to support monitoring activities.

All laboratory and clinical data gathered in this protocol will be stored in a password protected database. All patient information will be handled using synonymous identifiers. Linkage to patient identity is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

11.2 Related Tools, Software and/or Code

N/A

11.3 Standards

N/A

11.4 Data Preservation, Access, and Associated Timelines

N/A

11.5 Access, Distribution, or Reuse Considerations

N/A

11.6 Data Collection and Management Responsibilities

Data Capture: Data will be entered in the MD Anderson institutionally approved database (s). All eligibility criteria must be satisfied prior to treatment initiation.

All data collected will be used only for research purposes. Identifiers (name, medical record number, date of birth, treatment diagnosis, imaging tests, follow-up and death) may be collected **but will be replaced by study numbers in the analytic files.** Patient identifiers will be confidentially collected and securely maintained on a password protected server located behind the institutional firewall. Access to identifiers will follow IRB and MDA information security rules and regulations. The master database file will be accessible only to the Principal Investigator, approved collaborators, and research staff designated on the delegation of authority log.

Accuracy of Data Collection: The MD Anderson Principal Investigator will be the final arbiter of response and toxicity, should a difference of opinion exist.

11.7 Oversight of Data Management and Sharing

A protocol-specific monitoring plan will be developed by the IND Office.

11.8 Genomic Data Sharing Plan

N/A

11.9 Incidental/Secondary Findings Disclosure Procedure

N/A

12 STATEMENT OF COMPLIANCE

The trial will be conducted in compliance with the protocol and applicable state, local and federal regulatory requirements.

Each engaged institution must have a current Federal-Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) and must provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Institutional Review Board (IRB) or Ethics Committee (EC) registered with OHRP. Any amendments to the protocol or consent materials must also be approved before implementation.

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14 APPENDICES

A. Guidance for the Management of Anemia, Blood Cross-Matching, and Packed Red Blood Cell Transfusion Procedure

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.

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

After Exposure to Magrolimab

For all elective RBC and platelet transfusions, use leukocyte-reduced and gamma-irradiated units per institutional guidelines.

For RBC, phenotype/genotype matched units are preferred. However, CMV-seronegative units for CMV-seronegative patients will not be required for this study.

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

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

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

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

B. Guidance for the Management of Infusion Reactions and Late Hypersensitivity Reactions

Infusion-related reactions are defined by the NCI CTCAE as follows: a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances. The time frame for IRR assessment is the 24-hour period beginning from the start of the magrolimab infusion. Recommendations for the management of IRRs are provided below.

For Grade 1 symptoms (mild transient reaction; infusion interruption not indicated; intervention not indicated):

· Remain at bedside and monitor participant until recovery from symptoms.

For Grade 2 symptoms (infusion interruption indicated, but the participant responds promptly to symptomatic treatment [eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, IV fluids] and prophylactic medications indicated for ≤ 24 hours):

- Stop the magrolimab infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or 500 to 750 mg oral paracetamol/acetaminophen.
- Remain at bedside and monitor participant until resolution of symptoms.
- Corticosteroid therapy may also be administered 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 ensue after 60 minutes, the rate may be increased to 100% of the original infusion rate. Monitor the participant closely.
- If symptoms recur, then stop infusion and disconnect the participant from the infusion apparatus; no further magrolimab will be administered at that visit. The amount of study drug infused must be recorded on the case report form.
- Premedications should be considered before any future infusions.

- Participants who experience an IRR of Grade 2 during the postinfusion observation period that does not resolve during that time should be observed for 24 hours or until the AE resolves or stabilizes, with vital sign measurements and additional evaluations as medically indicated for the management of the AE.

For Grade 3 or Grade 4 symptoms where Grade 3 is described as prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates); and where Grade 4 is described as life-threatening consequences; urgent intervention indicated:

- Immediately discontinue infusion of magrolimab.
- Begin an IV infusion of normal saline, and treat the participant as follows: Administer bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.
- The participant should be monitored until the investigator is comfortable that the symptoms will not recur.
- Participants who have Grade 4 infusions occurring with the first dose will be permanently discontinued from treatment.
- Participants who have Grade 3 IRR with the first dose can be offered the opportunity to stay on study and must be given premedication prior to subsequent doses. In this setting, premedication with acetaminophen (650 to 1000 mg oral), diphenhydramine (25 to 50 mg oral or IV) and with dexamethasone (4 to 20 mg IV) as well, or comparable regimen, is recommended for the subsequent 2 doses. Long-term premedication can be discontinued if clinically indicated, for example, if the participant does not demonstrate further infusion reactions after multiple doses.
- Participants who receive premedication with corticosteroids and still have a Grade 3 or 4 infusion reaction will generally be permanently discontinued from treatment. However, specific study protocols should be followed for detailed guidance.
- Investigators should follow their institutional guidelines for the treatment of anaphylaxis.

In the case of late-occurring hypersensitivity symptoms (eg, appearance of localized or generalized pruritus after Day 1 but within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

A premedication regimen (oral acetaminophen and diphenhydramine, or comparable regimen) is required before the initial doses of magrolimab and in case of repriming of the participant after > 4 weeks interruption in magrolimab treatment. Specific premedication regimens for the combination therapies (cetuximab, rituximab, azacitidine, and avelumab) are described in the applicable study protocol.

C. Management of Pneumonitis

Pneumonitis has been infrequently observed in participants receiving magrolimab. Generally, immune-related AEs have not been observed in clinical use with magrolimab. In contrast to T-cell checkpoint inhibitors (eg, pembrolizumab), 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 related events of macrophage activation syndrome or hemophagocytic lymphohistiocytosis have been reported in clinical studies.

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

Management of potential pneumonitis is detailed in the Table below and follows Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline {Brahmer 2018}. Participants who experience Grade 3 or 4 pneumonitis will be permanently discontinued from study drug.

Table 18. Pneumonitis Management Algorithm

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

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

D. Magrolimab packaging, storage and handling

Magrolimab will be provided in aqueous solution in 10 mL vials for intravenous (IV) administration. The drug product will be shipped (refrigerated) to a clinical distribution and packaging site for storage and distribution. The magrolimab drug product will be shipped to MDACC pharmacy for dose preparation.

Vials containing magrolimab should be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) in an appropriate, locked room accessible only to pharmacy personnel, the principal investigator, or a duly designated person. Magrolimab should not be frozen and should be protected from light during storage. The drug product should not be shaken. Vials are single use containers and contain no preservatives; therefore, magrolimab administration should begin as soon as possible after preparation.

The clinical dose will be prepared (diluted in saline) as an IV infusion through a standard infusion set. Doses in the range of 0.1 to 60 mg/kg will be infused in volumes ranging from 250 to 500 mL. The durations of the IV infusions of magrolimab will be up to 3 hours for doses of 1 to 60 mg/kg. Initial priming doses will be infused over a 3-hour period.

The total exposure duration of the prepared magrolimab from the preparation start time and prior to the start of infusion, should not exceed:
- 16 hours at refrigerated temperature, between 2 to 8°C (36°F to 46°F), and/or
- 8 hours at room temperature (including equilibration time after refrigerated storage)

The prepared drug solution can be stored at refrigerated temperature between 2°C to 8°C (36°F to 46°F) for up to 16 hours and / or stored at room temperature for up to 8 hours from the preparation start time. If stored at refrigerated temperature, the prepared drug solution should be equilibrated to room temperature for at least 1 hour. The total room temperature exposure prior to start of infusion including equilibration time should not exceed 8 hours.

Solution Preparation and Administration

The desired amount of magrolimab should be withdrawn from the vial(s) and diluted in an infusion bag with 0.9% sodium chloride for injection. The bag should be gently inverted to mix the solution. Magrolimab drug product vials and the diluted solution should be inspected visually before administration. If particulate matter or any coloration is noted, drug should not be administered, and the sponsor should be notified.
Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures. Any unused study drug should be disposed of in accordance with local requirements.

Storage Conditions

Based on available stability data, the drug product should be stored at 2 °C to 8 °C and protected from light.

Stability

Gilead's policy is to monitor the stability of each formulation of study drug until the shelf life or a reevaluation period is established for the drug product. The stability studies cover the labeled

storage conditions and, as appropriate, accelerated conditions. The stability of the drug product is tested at prescribed intervals to support the shelf life. Studies under accelerated conditions serve to identify any stability trend ahead of its occurrence under the labeled storage conditions. Through the combined approach of accelerated condition studies and long-term stability monitoring with frequent testing, the purported identity, strength, and quality will be assured for all drug product lots used in clinical studies.