CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1b/2 Trial of Hu5F9-G4 in Combination with Rituximab or Rituximab + Chemotherapy in Patients with Relapsed/Refractory B-cell Non-Hodgkin's Lymphoma
Protocol Number:	5F9003
Investigational Products:	Hu5F9-G4 (magrolimab) in combination with rituximab and magrolimab in combination with rituximab, gemcitabine, and oxaliplatin
Indication:	Non-Hodgkin's Lymphoma
Development Phase:	1b/2
US IND Number:	118300
EudraCT Number:	2016-003408-29
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List
Investigator(s):	Ranjana Advani, M.D. Study Lead Principal Investigator Professor of Lymphoma, Stanford University 875 Blake Wilbur Drive Clinic C Stanford, CA 94305, USA Telephone: PPD Graham Collins, M.D. D.Sc. FMedSci United Kingdom Lead Principal Investigator Haemotology Consultant and Lymphoma Lead Oxford University Hospital Churchill Hospital Old Road, Headington, OX3 7LE United Kingdom

Amendment History:

Amendment 12 Date:	02 November 2023
Amendment 11 Date:	19 June 2023
Amendment 10 Date:	31 March 2022
Amendment 9 Date:	22 November 2019
Amendment 8 Date:	01 October 2018
Amendment 7 Date:	27 July 2018
Amendment 6 Date:	09 July 2018
Amendment 5 Date:	18 May 2017
Amendment 4 Date:	10 February 2017
Amendment 3 Date:	28 November 2016
Amendment 2 Date:	24 August 2016
Amendment 1 Date:	23 August 2016
Original Protocol Date:	14 July 2016

Compliance Statement:

This study will be conducted in accordance with Protocol 5F9003, the International Conference on Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and the applicable country and regional (local) regulatory requirements.

PROTOCOL APPROVAL PAGE

I have read the document described above, and my signature below indicates my approval:

[See appended electronic signature]

PPD

Senior Associate Director, Clinical Development
Gilead Sciences

Date

PROTOCOL ACCEPTANCE PAGE

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), the Declaration of Helsinki, my local and regional clinical trial regulatory requirements (including the Code of Federal Regulations [CFR] Title 21), and the clinical trial protocol. I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Investigator's Name: _____

Name of Institution/Site: _____

Signature: _____

Date: _____

SUMMARY OF CHANGES, PROTOCOL 5F9003 AMENDMENT 12

The primary reason for this amendment is to incorporate new safety management information from the current investigator's brochure (IB).

The major updates to the protocol and related rationale are as follows:

- Section 1.6.1 was updated to clarify known hematological toxicities associated with magrolimab and rituximab and provides a link to the Section 6.2. In alignment with current safety data from magrolimab IB Edition 12, language was updated to replace language stating "no significant overlapping toxicities between magrolimab and rituximab have been observed in patients on this trial (data on file)" with language stating "to date, the safety profile of magrolimab in combination with rituximab has been shown tolerable".
- Section 1.6.3 was updated to remove the language related to "no overlapping myelosuppression toxicity" in alignment with the current safety data from magrolimab IB Edition 12.
- Section 6.1.1.2 and was updated to incorporate dexamethasone into the premedication regimen guidance before the first 2 doses of magrolimab or in the case of reintroduction with repriming to align with magralimab IB Edition 12.
- Section 6.2.1.3 was updated to incorporate dexamethasone into premedication guidance for safety management in case of Grade 3 or Grade 4 infusion related reaction (IRR) to align with magralimab IB Edition 12.
- Section 6.2.1.3 was updated to incorporate guidelines for safety management in case of severe neutropenia and serious infections.
- Section 6.2.1.3 toxicity management was clarified applying to Grade 1 and Grade 2 IRRs to include language that patients who experience IRRs with the first 2 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion.
- Section 6.2.1.3 was updated to clarify that patients who receive premedication and still experience a recurrent Grade 3 IRR or who experience a Grade 4 infusion reaction at any time will be permanently discontinued from study treatment.
- Section 6.2.1.3 was updated to clarify that the premedication starting dose of oral acetaminophen to to be 650 mg in case of Grade 3 infusion reactions to align with safety management guidance in the IB.
- Section 12.14 (Publication Policy) was removed as Gilead does not have a publication charter.

Additional change(s) to the protocol include the following:

- Administrative, editorial, formatting updates, changes, corrections, and clarifications were made throughout, where appropriate.

PROTOCOL SYNOPSIS

Sponsor: Gilead Sciences, Inc.

Investigational Agents: Hu5F9-G4 (magrolimab) in combination with rituximab (magrolimab + rituximab, “antibody combination”) and magrolimab in combination with rituximab, gemcitabine, and oxaliplatin (magrolimab + R-GemOx, “chemotherapy combination”)

Protocol Number: 5F9003 Amendment 12

Study Title: A Phase 1b/2 Trial of Hu5F9-G4 in Combination with Rituximab or with Rituximab + Chemotherapy in Patients with Relapsed/Refractory B-cell Non-Hodgkin’s Lymphoma

Study Objectives and Endpoints

Synopsis Table 1 Study Objectives and Endpoints

PRIMARY	
Objectives	**Endpoints**
• To investigate the safety and tolerability, and to define the RP2DS for magrolimab in combination with rituximab and for magrolimab in combination with R-GemOx • To evaluate the efficacy of magrolimab in combination with rituximab in patients with indolent lymphoma and DLBCL and to evaluate the efficacy of magrolimab in combination with R-GemOx in ASCT ineligible DLBCL as measured by the ORR according to Lugano Classification for lymphomas (Cheson 2014; Table 10-1)	• DLTs (Phase 1b only [in the antibody combination (magrolimab + rituximab) and the chemotherapy combination (magrolimab + R-GemOx) cohorts]) and AEs according to NCI CTCAE, Version 4.03 • ORR as defined by the Investigator according to the Lugano Classification for lymphomas (Table 10-1)

SECONDARY	
Objectives	**Endpoints**
• To evaluate the PK profiles of magrolimab in combination with rituximab and magrolimab in combination with R-GemOx • To evaluate the immunogenicity of magrolimab in combination with rituximab and magrolimab in combination with R-GemOx • To evaluate the efficacy of magrolimab in combination with rituximab in indolent lymphoma and DLBCL and magrolimab in combination with R-GemOx in ASCT ineligible DLBCL as measured by the DOR, PFS, OS, and TTP • To evaluate the efficacy of magrolimab in combination with rituximab in patients with indolent lymphoma and DLBCL and magrolimab in combination with R-GemOx in ASCT ineligible DLBCL as measured by ORR according to LYRIC (Cheson 2016; Table 10-2)	• Concentration versus time measurements for magrolimab in combination with rituximab and for magrolimab in combination with R-GemOx and their PK parameters including C_{max} and AUC • ADAs to magrolimab in combination with rituximab and magrolimab in combination with R-GemOx • DOR, PFS, OS, and TTP • ORR as defined by the Investigator according to the LYRIC criteria for lymphomas (Table 10-2)

Overall Study Design

This trial is an open-label, multicenter, Phase 1b/2 trial investigating magrolimab + rituximab (antibody combination) in R/R B-cell non-Hodgkin's lymphoma (NHL) and magrolimab + rituximab, gemcitabine, and oxaliplatin (R-GemOx; chemotherapy combination) in indolent lymphoma and diffuse large B-cell lymphoma (DLBCL) (refer to the Study Design Schema).

Antibody Combination: Magrolimab + Rituximab

Phase 1b: Dose escalation and regimen exploration for patients with B-cell NHL
Phase 2: Treatment cohorts evaluating RP2DS and alternate dose regimens (indolent lymphoma and DLBCL)

Chemotherapy Combination: Magrolimab + R-GemOx

Phase 1b: This cohort will be conducted in a safety dose-escalation phase followed by an expansion phase in high-dose chemotherapy and autologous stem cell transplant (ASCT) ineligible DLBCL.

Clinical Trial Steering Committee

The Clinical Trial Steering Committee (CTSC) will oversee the conduct of the clinical trial. The composition, structure, and function of the CTSC are defined in the CTSC Charter.

Duration of Treatment

Magrolimab + rituximab treatment may be continued until loss of clinical benefit or unacceptable toxicity for patients who do not have disease progression. Gemcitabine and oxaliplatin dosing are intended to complete after Cycle 4; however, dosing may continue beyond Cycle 4, as needed, until a total of 8 doses have been received at the discretion of the Investigator. Patients who do not tolerate one of the study treatment drugs may continue the other study treatment drug(s) for the duration of the trial, if the Sponsor and Principal Investigator agree.

Overview of Assessments

Assessments will be conducted according to the schedules provided in Section 7.1.

Translational Studies

Samples will be collected according to the schedules provided in Section 7.1.

Correlative studies will be performed on peripheral blood samples to determine the biologic activity of magrolimab in combination with rituximab or R-GemOx on circulating immune cells and molecular subtypes of NHL. These studies may include, but are not limited to, investigations of plasma cytokine levels, characterization of circulating T cells, and characterization of circulating tumor or cell-free DNA.

Planned Number of Patients

Study Total: Up to 422 patients may be enrolled to ensure sufficient efficacy-evaluable patients across all cohorts.

Phase 1b:
Antibody Combination: Magrolimab + Rituximab

25 to 38 patients (total planned)

Planned patients per dose level (potential for expansion in each cohort of up to 16):

Level 1: 3 to 6
Level 2: 3 to 6
Level 3: 3 to 6
Level 4: 3 to 6

Chemotherapy Combination: Magrolimab + R-GemOx
29 to 68 patients (total planned)
Safety dose escalation: 9 to 48 (2 planned dose levels, 2 dose de-escalation levels)
Expansion: 20

Phase 2:

Up to 316 evaluable patients for efficacy (up to 108 patients with indolent lymphoma; up to 208 patients with DLBCL).

Inclusion Criteria

1. Adults ≥ 18 years.
2. Antibody combination (magrolimab + rituximab) Phase 1b cohort only: B-cell NHL expressing CD20 by immunohistochemistry (IHC) or flow cytometry, relapsed or refractory to at least 2 prior lines of therapy.
3. DLBCL chemotherapy combination (magrolimab + R-GemOx) Phase 1b safety dose-escalation and expansion cohorts:
   a. Histologically confirmed de novo or transformed DLBCL relapsed or refractory to 1 to 3 prior lines of therapy who are not candidates for high-dose chemotherapy and autologous stem cell transplantation (ASCT). Patients relapsed after ASCT are allowed.
   b. At least 1 prior therapy must have included a CD20-targeted therapy.
   c. Primary refractory patients are excluded as defined by failure to achieve a partial response (PR) or complete response (CR) to frontline therapy or progression within 3 months of completing treatment.
   d. The 1 to 3 prior lines of therapy requirement is only applicable for treatment regimens for DLBCL and not for prior lymphomas in the case of transformed DLBCL.
4. For the DLBCL antibody combination (magrolimab + rituximab) Phase 2 Cohort 4, de novo or transformed DLBCL, not otherwise specified, according to the World Health Organization 2016 classification of lymphoid neoplasms (Swerdlow 2016) expressing CD20 by IHC or flow cytometry, that is relapsed or refractory to at least 2 prior lines of therapy containing and anti-CD20 therapy.

   Prior autologous hematopoietic cell transplantation is permitted.

5. Indolent lymphoma Phase 2 Cohort: Histologically confirmed marginal zone or follicular lymphoma (Grade 1 to 3a) expressing CD20 by IHC or flow cytometry, relapsed or refractory to at least 2 prior lines of therapy.
6. Eastern Cooperative Oncology Group (ECOG) score 0 to 2.
7. Disease that is measurable or assessable for response per Lugano Classification for lymphomas (Cheson 2014; Table 10-1).
8. Laboratory measurements, blood counts:
   - Hemoglobin must be $\geq$ 9 g/dL within 24 hours prior to the first 2 doses of magrolimab infusion. NOTE: Transfusions are allowed to meet hemoglobin eligibility (see Section 6.2.1.3 for anemia management).
   - Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/mL
   - For the antibody combination (magrolimab + rituximab) Phase 1b and Phase 2 cohorts: Platelets $\geq 50 \times 10^9$/mL.
   - For the Phase 1b chemotherapy combination (magrolimab + R-GemOx) safety dose-escalation and expansion cohorts only, platelets $\geq 100 \times 10^9$/mL.
9. Laboratory measurements, hepatic function:
   - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) < 5 × upper limit of normal (ULN).
   - Bilirubin ≤ 1.5 × or 3.0 × ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or a genetic equivalent.
10. Laboratory measurements, renal function:
    - Serum creatinine ≤ 1.5 × ULN or calculated glomerular filtration rate (GFR) > 40 mL/min/1.73 m^2.
11. Women of childbearing potential (WOCBP) must not be nursing or planning to be pregnant and must have a negative urine or serum pregnancy test within 30 days before enrollment and within 72 hours before the first administration of magrolimab.
12. WOCBP must be willing to use at least 1 highly effective method of contraception during the study and continue for 4 months after the last dose of magrolimab and 12 months after the last dose of rituximab.
13. Male patients who are sexually active with a WOCBP and who have not had vasectomies must be willing to use a barrier method of contraception and refrain from sperm donation during the study and for 4 months after the last dose of magrolimab and 12 months after the last dose of rituximab. If the partner is pregnant, male patients must use barrier method contraception (condom) during the study and for 4 months after the last dose of magrolimab and until there is a pregnancy outcome (whichever is applicable) to prevent fetal exposure to study drugs.
14. Patient has provided informed consent.
15. Must be willing and able to comply with clinic visits and procedures outlined in the study protocol.

16. DLBCL chemotherapy combination (magrolimab + R-GemOx) Phase 1b safety dose-escalation and expansion cohorts and Phase 2 antibody combination (magrolimab + rituximab) indolent lymphoma and DLBCL cohorts: Willing to consent to 1 mandatory pretreatment and 1 on-treatment tumor biopsy, unless determined to not be feasible by the Investigator (Reasons include, but are not limited to, lack of accessible tumor tissue to biopsy and patient safety issues.)
17. CAR-T naïve or CAR-T ineligible patients and otherwise meet other inclusion/exclusion criteria may enroll. Patients who relapse following CAR-T therapy are not eligible.

Exclusion Criteria

1. Patients with active brain metastases. (Patients with stable treated central nervous system [CNS] lesions who are off corticosteroid therapy for at least 3 weeks are not considered active.)
2. Prior allogeneic stem cell transplant.
3. Prior anti-cancer therapy, including chemotherapy, hormonal therapy, and investigational agents within 3 weeks or within at least 4 half-lives prior to magrolimab dosing (up to a maximum of 4 weeks), whichever is longer.

   NOTE: Low dose steroids (oral prednisone or equivalent ≤ 20 mg per day), localized non-CNS radiotherapy, previous hormonal therapy with luteinizing hormone-releasing hormone (LHRH) agonists for prostate cancer, and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors are not criteria for exclusion.
4. Known active or chronic hepatitis B or C infection or human immunodeficiency virus (HIV).
5. Red blood cell (RBC) transfusion dependence, defined as requiring more than 2 units of RBC transfusions during the 4-week period prior to screening. RBC transfusions are permitted during screening and prior to enrollment to meet the hemoglobin inclusion criteria.
6. History of hemolytic anemia or Evans syndrome in the last 3 months.
7. Positive IgG component of the direct antiglobulin test (DAT).
8. Prior treatment with CD47 or signal regulatory protein alpha (SIRPα)-targeting agents.
9. Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancy for which patients are not on active anti-cancer therapy as defined in Exclusion Criterion 3.
10. Hypersensitivity to the active substance, to murine proteins, or to any of the other excipients of rituximab listed in Appendix A.
11. Significant medical diseases or 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, severely immunocompromised state, and congestive heart failure New York Heart Association (NYHA) Class II-IV.

12. History of psychiatric illness or substance abuse likely to interfere with ability to comply with protocol requirements or give informed consent.
13. Pregnancy or active breastfeeding.
14. Additional exclusion criteria for DLBCL chemotherapy combination (magrolimab + R-GemOx) Phase 1b safety dose-escalation and expansion cohorts only:
    a. Undergone ASCT within a period of ≤ 3 months before signing informed consent.
    b. Prior treatment with gemcitabine and oxaliplatin. However, patients who relapse ≥ 12 months after treatment with a gemcitabine and oxaliplatin-containing regimen are allowed.
    c. Known hypersensitivity to gemcitabine, oxaliplatin, or other platinum compounds.
    d. Intolerance of gemcitabine, oxaliplatin, and/or rituximab as monotherapy or in combination due to unacceptable toxicities as determined by the treating Investigator.

Test Product, Dose, and Mode of Administration

Magrolimab is a humanized IgG4 monoclonal antibody (mAb) of the IgG4 kappa isotype containing a Ser-Pro (S-P) substitution in the hinge region (position 228) of the heavy chain to reduce Fab arm exchange. Magrolimab is a humanized mAb against CD47.

Rituximab is a genetically engineered chimeric murine/human monoclonal IgG_1 kappa antibody directed against the CD20 antigen.

Gemcitabine is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine HCl is 2´-deoxy-2´,2´-difluorocytidine monohydrochloride (β-isomer).

Oxaliplatin is an antineoplastic agent. It is an organoplatinum complex in which the platinum atom is complexed with 1,2-diaminocyclohexane and with an oxalate ligand as a leaving group.

Dosing Regimens:
Antibody Combination: Magrolimab + Rituximab, Phase 1b

In Phase 1b, magrolimab was administered on Days 1, 8, 15, and 22 for all cycles (cycle length is 28 days). In Phase 1b, rituximab was administered on Days 8, 15, and 22 for the first cycle and then on Day 1 for Cycles 2 through 6. Rituximab dosing was extended beyond Cycle 6 in a protocol amendment letter.

Antibody Combination: Magrolimab + Rituximab, Phase 2 (Amendment 9)

Synopsis Table 2 Dosing: Antibody Combination (Magrolimab + Rituximab) Phase 2 Cohort 4

Drug/Dose (IV)	Dose Schedule (Day per 28-day Cycle)			
	Cycle 1	Cycle 2	Cycles 3 to 6	Cycle 7+
Magrolimab 1 mg/kg (prime) Magrolimab 30 mg/kg (maintenance)[a]	Day 1 Day 8[a], 15, 22	— Day 1, 8, 15, 22	— Day 1,15	— Day 1, 15
Rituximab 375 mg/m^2 [a]	Day 8[a], 15, 22	Day 1	Day 1 of Cycle 6, then Day 1 every other Cycle starting Cycle 8	

Abbreviations: IV = intravenous.

a. On Cycle 1 Day 8, magrolimab is to be given first followed by rituximab. For all other times when rituximab and magrolimab are given on the same visit, rituximab should be given first. There should be at least an hour interval between the end of infusion of the first drug and the beginning of the infusion of the second drug.

Chemotherapy Combination: Magrolimab + R-GemOx, Phase 1b

Synopsis Table 3 Chemotherapy Combination (Magrolimab + R-GemOx) Safety Dose-Escalation and Expansion Cohorts

Drug	Cycle 1 (5 weeks)	Cycle 2 (4 weeks)	Cycles 3 to 4 (4 weeks)	Cycles 5 to 6 (4 weeks)	Cycle 7+ (4 weeks)
DOSE-ESCALATION **Dose Level 1: Magrolimab (IV)[a]**	1 mg/kg priming: Day 1 30 mg/kg maintenance: Day 8, 11, 15, 22, 29	30 mg/kg maintenance: Day 1, 8, 15, 22	30 mg/kg maintenance: Day 1, 15	30 mg/kg maintenance: Day 1, 15	30 mg/kg maintenance: Day 1, 15
DOSE-ESCALATION **Dose Level 2: Magrolimab (IV)[b]**	1 mg/kg priming: Day 1 45 mg/kg maintenance: Day 8, 11, 15, 22, 29	45 mg/kg maintenance: Day 1, 8, 15, 22	45 mg/kg maintenance: Day 1, 15	45 mg/kg maintenance: Day 1, 15	45 mg/kg maintenance: Day 1, 15
DOSE-EXPANSION **Magrolimab (IV)[c,d]**	1 mg/kg priming: Day 1 30mg/kg maintenance: Day 8[d], 15, 22, 29	30 mg/kg maintenance: Day 1, 8, 15, 22	30 mg/kg maintenance: Day 1, 15	30 mg/kg maintenance: Day 1, 15	30 mg/kg maintenance: Day 1, 15

Drug	Cycle 1 (5 weeks)	Cycle 2 (4 weeks)	Cycles 3 to 4 (4 weeks)	Cycles 5 to 6 (4 weeks)	Cycle 7+ (4 weeks)
Rituximab (IV)[d]	375 mg/m^2: Day 8[d], 15, 22, 29	375 mg/m^2: Day 1	375 mg/m^2: Day 1	375 mg/m^2: Day 1 then Day 1 every other cycle starting Cycle 8	-
Gemcitabine (IV)	1000 mg/m^2: Day 11, 23	1000 mg/m^2: Day 2, 15	1000 mg/m^2: Day 2, 15	-	-
Oxaliplatin (IV)	100 mg/m^2: Day 11, 23	100 mg/m^2: Day 2, 15	100 mg/m^2: Day 2, 15	-	-
G-CSF prophylaxis[e]	Administer	Administer	Administer	-	-
Allopurinol (oral)[f]	Daily	-	-	-	-

Abbreviations: CTSC = Clinical Trial Steering Committee; G-CSF = granulocyte colony stimulating factor; IV = intravenous; R-GemOx = rituximab, gemcitabine, and oxaliplatin.

a. Magrolimab maintenance dose maybe de-escalated to 20 mg/kg or 10 mg/kg with the identical dosing schedule of maintenance doses if the regimen is deemed too toxic by the CTSC.

b. The CTSC may decide to explore higher doses of magrolimab in increments up to 50% higher than theprior dose level deemed to be safe in accordance with the modified 3 + 3 design.

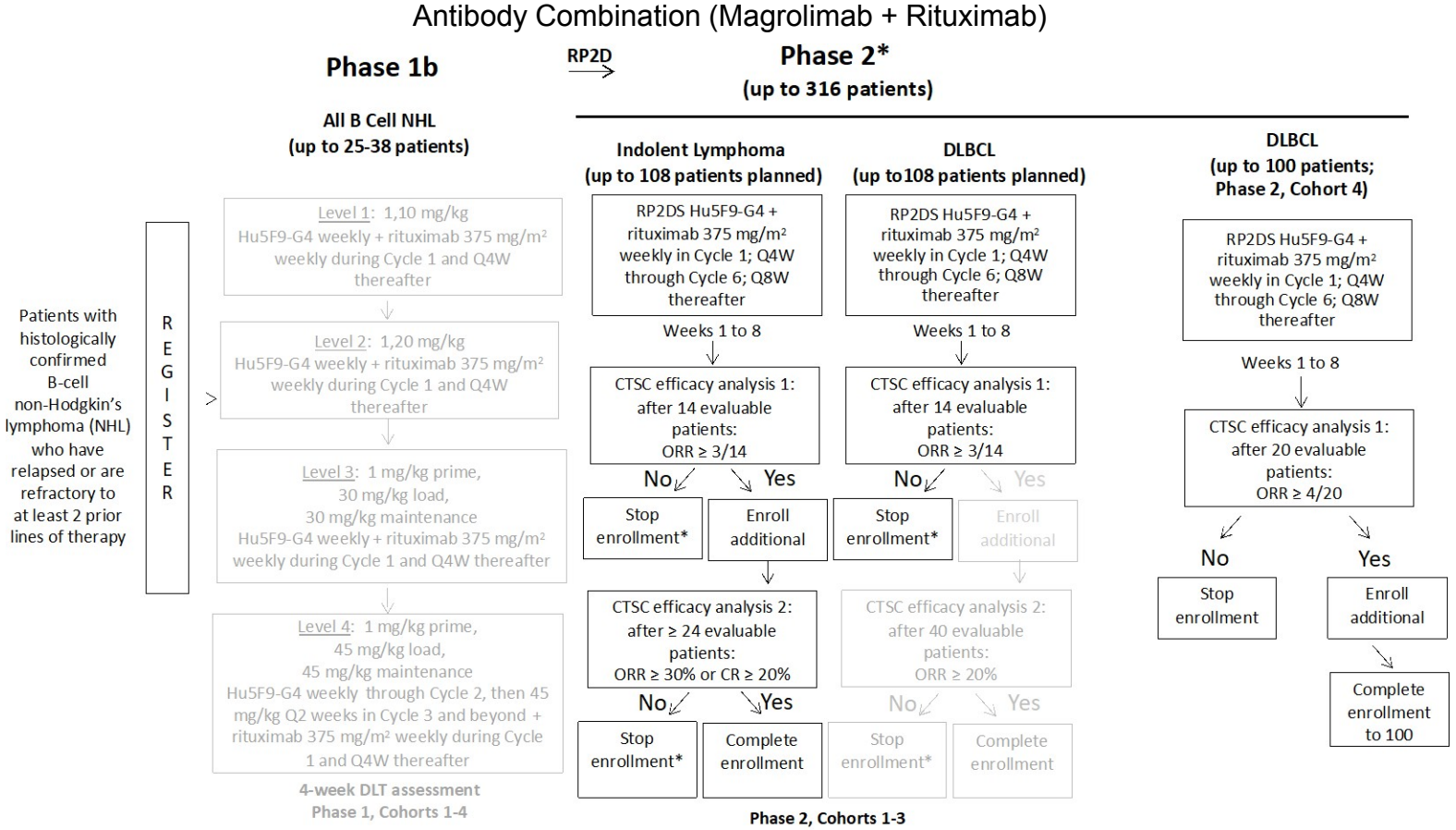
c. The magrolimab maintenance dose level utilized in the expansion phase will be the recommended dose selected by the CTSC from the safety dose-escalation phase.

d. On Cycle 1 Day 8, magrolimab is to be given first followed by rituximab. For all other times when rituximab and magrolimab are given on the same visit, rituximab should be given first. There should be at least an hour interval between the end of infusion of the first drug and the beginning of the infusion of the second drug.

e. G-CSF primary prophylaxis must be administered with gemcitabine and oxaliplatin treatment. Local standard of care or equivalent will be administered in accordance to local institutional guidelines or Investigator guidance. G-CSF prophylaxis should generally occur within several days after administration of each day gemcitabine and oxaliplatin is dosed. However, the timing of G-CSF prophylaxis may be given in accordance to local institutional guidelines.

f. Allopurinol of 300 mg oral daily should be administered for the first cycle only to prevent tumor lysis syndrome associated with chemotherapy. Allopurinol may be given at 100 mg oral daily for the first cycle if significant renal impairment is present as determined by the Investigator.

STUDY DESIGN SCHEMA



*An alternative dose regimen may be evaluated in additional patients as determined by the CTSC.
Gray texts indicates completed or on-hold as of Amendment 9.

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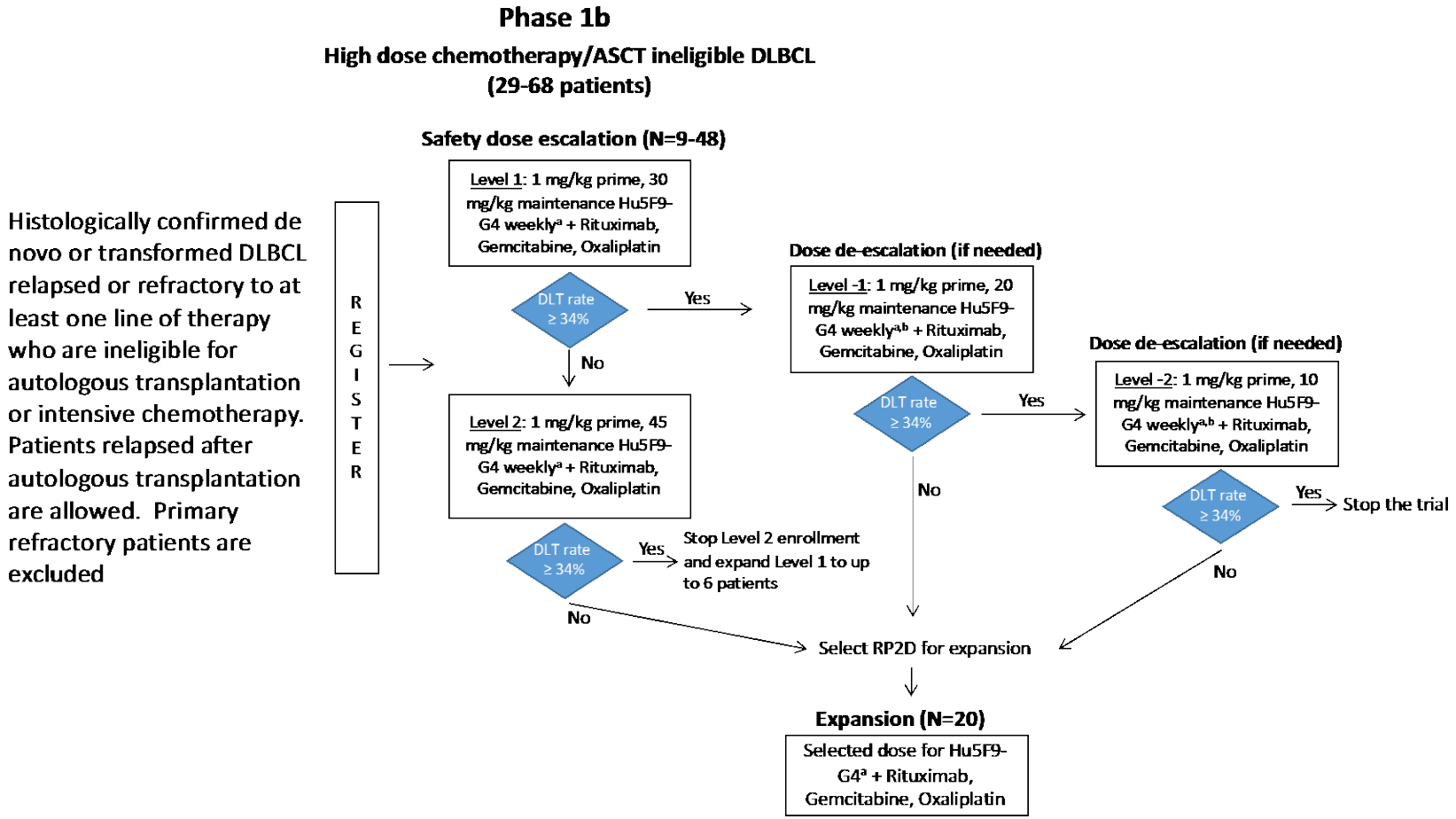
Chemotherapy Combination (Magrolimab +R GemOx)



Abbreviations: ASCT = autologous stem cell transplant; CR = complete response; CTSC = Clinical Trial Steering Committee; DLBCL = diffuse large B-cell lymphoma; DLT = dose-limiting toxicity; MTD = maximum tolerated dose; NHL = non-Hodgkin's lymphoma; ORR = objective response rate; Q4W = every 4 weeks; Q8W = every 8 weeks; RP2DS = recommended Phase 2 dose and schedule.

a. Refer to Table 6-3 for specific magrolimab dosing regimens.
b. Dose de-escalation to dose level -2 may further occur using a 1 mg/kg magrolimab priming dose and 10 mg/kg maintenance doses if the MTD is exceeded at dose level -1.

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ABBREVIATIONS AND DEFINITIONS

Term	Definition
5PS	5-point scale
ADA	anti-drug antibody
ADL	activities of daily life
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
ASCT	autologous stem cell transplant (or transplantation)
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{last}	AUC from time zero to the last measurable concentration sampling time (t_{last}) (mass × time ×volume - 1)
AUC_{tau}	AUC calculated to the end of a dosing interval (tau) at steady state (amount × time × volume - 1)
AZA	azacitidine
BLQ	below the limit of quantitation
BUN	blood urea nitrogen
CAR-T	chimeric antigen receptor
CBC	complete blood count
CFR	Code of Federal Regulations
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
C_{max}	maximum concentration observed
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CRF	case report form (paper)
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTSC	Clinical Trial Steering Committee
CV	coefficient of variation
CyTOF	mass cytometry
DAT	direct antiglobulin test
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EAS	Efficacy Analysis Set
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture

Term	Definition
EGA	4-bromobenzaldehyde N-(2,6-dimethylphenyl) semicarbazone
EOT	end-of-treatment
Fc	fragment, crystallizable
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FL	follicular lymphoma
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
INR	international normalized ratio
IR	indeterminate response
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous
IWRS	interactive web response technology
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LDi	longest diameter of a lesion
LHRH	luteinizing hormone-releasing hormone
LISS	low-ionic-strength solution
LYRIC	LYmphoma Response to Immunomodulatory Therapy Criteria
M1	macrophages that suppress tumor progression
M2	macrophages that promote tumor progression
mAb	monoclonal antibody
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary of Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
Min	minutes
MNS	a human blood group system based on 2 genes (glycophorin A and glycophorin B) on chromosome 4
MOA	mechanism of action
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
No.	number
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma

Term	Definition
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic
PE	physical examination
PeG	polyethylene glycol
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PKPD	Pharmacokinetic and pharmacodynamic
PPD	cross product of the LDi and perpendicular diameter
PR	partial response
PT	prothrombin time
Q2C	every 2 cycles
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
RANKL	receptor activator of nuclear factor kappa-B ligand
RBC	red blood cell(s)
REC	Research Ethics Committee
R-GemOx	rituximab, gemcitabine, and oxaliplatin
Rh	Rhesus factor
RNA	ribonucleic acid
RP2DS	recommended Phase 2 dose and schedule
R/R	relapsed/refractory
RO	receptor occupancy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAF	Safety Analysis Set
SD	standard deviation
SDi	shortest axis perpendicular to the LDi
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIRPα	signal regulatory protein alpha
SOA	Schedule of Assessments
SPD	sum of the product of diameters
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
TTP	time to progression
ULN	upper limit of normal
UK	United Kingdom
US	United States
USP	United States Pharmacopeia
WBC	white blood cell
WOCBP	women of childbearing potential

1. BACKGROUND

1.1. Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma (NHL) is among the most common cancers in the United States (US) and Europe with more than 70,000 and 93,000 new cases diagnosed every year, respectively (Ferlay 2015). NHL is a heterogeneous group of malignancies with varying clinical characteristics that are optimally managed through a range of different treatment modalities. The spectrum of NHL includes more indolent variants such as follicular and marginal zone lymphomas, to more aggressive subtypes such as diffuse large B-cell lymphoma (DLBCL). While systemic chemotherapy is a mainstay of treatment for most NHL variants, antitumor directed monoclonal antibodies (mAb) have an important role in the treatment of this disease (Oflazoglu 2010). Antibodies such as rituximab, which targets the B-cell antigen CD20, are now part of the standard treatment regimens for many B-cell NHLs (Keating 2010). However, once NHL becomes refractory to standard chemotherapy and antibody-based therapies, the overall prognosis is poor, with limited long-term survival. Thus, novel and effective therapies are needed to address this high unmet medical need.

1.1.1. Indolent Lymphoma

Indolent lymphomas represent 40% of all NHL subtypes, with follicular lymphoma (FL) occurring with the greatest frequency (Harris 1999). Indolent lymphomas present with a broad spectrum of disease characteristics. Patients often experience a chronic relapsing and remitting disease course and are exposed to several successive treatment regimens, resulting eventually in death due to disease progression. In general, treatment is reserved for patients who develop significant symptoms or who are sufficiently high risk to merit early therapy (Gribben 2007).

The most common frontline therapies include a combination of alkylators (including cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP] or bendamustine) in combination with the anti-CD20 mAb rituximab. In addition,

single agent rituximab is also often administered as frontline therapy, particularly in patients with lower disease burden or who may not tolerate combination chemo- immunotherapy (Sousou 2010). Rituximab was originally approved for use in patients with relapsed and refractory FL and low grade lymphoma. For patients with indolent NHL who initially respond (complete response [CR] or partial response [PR] with a time to progression [TTP] of at least 6 months) and then experience relapse after single-agent rituximab, retreatment with either rituximab alone or in combination with chemotherapy is frequently given (Kahl 2014; Gribben 2007; NCCN Guidelines Version 3 2016). Patients who become refractory to rituximab alone or in combination with chemotherapy have limited options for effective treatment.

One approach to enhancing the efficacy of rituximab is the addition of other biologic agents that could potentiate its activity. There is strong nonclinical evidence demonstrating that Hu5F9-G4 (magrolimab), an anti-CD47 antibody, can synergize with rituximab to eliminate both the indolent and aggressive lymphoma subtypes (Chao 2010a).
After exploring clinical proof of concept of the combination of magrolimab with rituximab to treat indolent and aggressive NHL, this trial may be expanded to explore efficacy.

1.1.2. Diffuse Large B-cell Lymphoma

DLBCL is an aggressive subtype of NHL that accounts for approximately 30% of all NHL (Non-Hodgkin's Lymphoma Classification Project 1997). Combination chemotherapy with the addition of rituximab is standard of care for patients with newly diagnosed DLBCL. However, approximately 40% of patients with DLBCL relapse following initial immunochemotherapy (Vaidya 2014).

For patients who are eligible, salvage chemotherapy regimens followed by autologous stem cell transplantation (ASCT) is standard of care; although, many patients are not eligible for transplantation due to age and other medical co-morbidities. While multiple salvage regimens comprising combination

chemotherapy are available for relapsed/refractory (R/R) disease, no standard salvage regimen exists currently. The development of more effective therapies for R/R DLBCL represents a high unmet medical need. In addition to indolent lymphoma, this study will investigate the use of an anti-CD47 antibody, magrolimab, in combination with rituximab for patients with DLBCL.

In DLBCL patients who relapsed or did not respond to frontline rituximab-chemotherapy combination, treatment with high-dose salvage chemotherapy with rituximab with subsequent ASCT is typically standard of care. Patients who relapse or are refractory after at least 2 lines of therapy are eligible for CAR-T cell therapy. However, a significant percentage of patients are not eligible for high-dose chemotherapy, ASCT, or CAR-T cell therapy due to a combination of age, co-morbidities, or failure to achieve a response to rituximab + salvage chemotherapy. These transplant-ineligible DLBCL patients have a poor prognosis (Mounier 2013) and treatment options are limited. When treatment is indicated, lower intensity salvage chemotherapies in combination with rituximab are generally administered that include rituximab, gemcitabine, and oxaliplatin (R-GemOx) or rituximab + bendamustine (Merchionne 2014). In transplant-ineligible DLBCL patients, R-GemOx is often used as a lower intensity treatment option compared with rituximab + bendamustine, given its lower myelosuppression rates, better tolerability, and similar ability to induce clinical responses (Mounier 2013; Merchionne 2014). However, significant clinical benefit with R-GemOx and other rituximab/salvage chemotherapies is limited due lack of durable responses. More effective treatment options that build on R-GemOx and other rituximab salvage chemotherapy regimens are needed.

1.2. Magrolimab

1.2.1. Nonclinical Background

The Stanford researchers in the laboratories of Weissman and Majeti have identified CD47 as a key molecule mediating cancer cell evasion of phagocytosis by the innate immune system. CD47 appears to be an indispensable means by which cancer cells, including cancer stem cells, overcome intrinsic expression of their

prophagocytic, “eat me,” signals (Jaiswal 2009; Majeti 2009). The Weissman laboratory have found that CD47 expression is increased on the surface of cancer cells from a large number of diverse human tumor types. Additional background information can be found in the most recent Investigator’s Brochure (IB).

A mAb targeting CD47 enables selective phagocytosis and elimination of tumor cells, but not normal cells, and is a potentially beneficial therapy for NHL. CD47-blocking antibodies have been shown to exhibit potent synergy with tumor-specific mAbs, such as the anti-CD20 antibody rituximab in NHL. In nonclinical models of NHL (including both indolent lymphoma and DLBCL), anti-CD47 antibody synergized with rituximab to yield dramatic levels of tumor phagocytosis in vitro compared to either monotherapy. This mechanism of synergy was due to the engaging of 2 mechanisms of phagocytosis: anti-CD47 antibody-mediated phagocytosis through inhibition of CD47-signal regulatory protein alpha (SIRPα) signaling and rituximab-mediated phagocytosis through delivery of a pro-phagocytic signal through the fragment, crystallizable (Fc) receptor leading to antibody-dependent cellular phagocytosis (Chao 2010a). These nonclinical experiments provide the rationale for the use of anti-CD47 antibody in combination with rituximab for the treatment of patients with B-cell NHL.

The activity of magrolimab is primarily dependent on blocking CD47 binding to SIRPα and not on the recruitment of Fc-dependent effector functions, although the presence of the immunoglobulin (Ig)G4 Fc domain is required for its full activity. For this reason, magrolimab was engineered with a human IgG4 isotype that is relatively inefficient at recruiting Fc-dependent effector functions that might enhance toxic effects on normal CD47 expressing cells (Liu 2015b). Nonclinical studies using xenograft cancer models provide compelling evidence that magrolimab triggers phagocytosis and elimination of cancer cells from human solid tumors and hematologic malignancies. Based on this mechanism of action (MOA) and its potent nonclinical activity, magrolimab is being developed as a novel therapeutic candidate for solid tumors and hematologic malignancies.

Most normal cells lack expression of pro-phagocytic signals and are unaffected by magrolimab. Red blood cells (RBCs) are a notable exception because CD47 expression protects RBCs from elimination by splenic macrophages, as well as sinusoidal macrophages, in liver and bone marrow. As RBCs age, they lose CD47 expression and reorganize membrane phospholipids in a manner that enhances pro-phagocytic signaling, leading to their elimination. Administration of magrolimab accelerates this process by substituting gradual loss of CD47 with immediate blockade of CD47 on aging RBCs, changing the balance between anti-phagocytic and pro-phagocytic signals. In nonclinical studies, the premature loss of aging RBCs is compensated by an ensuing reticulocytosis, and the initial anemia resolves as aged RBCs are replaced with younger cells. The potential for severe anemia is ameliorated by administration of a low priming dose of the antibody that results in mild-to-moderate anemia and stimulates reticulocytosis.

The combination of magrolimab and rituximab represents a novel treatment modality that can induce synergistic antitumor responses in B-cell NHL nonclinical models. These data serve as the basis for the evaluation of this combination in B-cell NHL patients. The addition of chemotherapy to magrolimab can lead to enhanced tumor phagocytosis through induction of pro-phagocytic signals. These observations support the rationale for an additional combination of R-GemOx with magrolimab in patients with NHL.

1.2.2. Clinical Background

Magrolimab has been administered as monotherapy and in combination with other antitumor compounds in clinical trials. A summary of the clinical safety and efficacy data from ongoing human clinical trials with magrolimab is presented in the most recent magrolimab IB, including data from Studies SCI-CD47-001 (solid tumor), SCI-CD47-002 (acute myeloid leukemia [AML]), 5F9003 (this study in NHL), 5F9004 (colorectal cancer [CRC]), and 5F9006 (ovarian cancer). Magrolimab has been administered as monotherapy and in combination with other antitumor compounds in clinical trials. Refer to the IB for additional information.

1.2.2.1. Summary of Magrolimab Clinical Safety

As of 24 July 2019, more than 400 patients have been treated with magrolimab as monotherapy or in combination. The most common treatment-related adverse events (TRAEs) were anemia, fatigue, headache, infusion-related reaction (IRR), pyrexia, chills, nausea, RBC agglutination, and vomiting.

Generally, magrolimab has an acceptable safety profile across all clinical studies with no maximum tolerated dose (MTD) reached with up to 45 mg/kg of weekly dosing as monotherapy and in combination (Study SCI-CD47-001 data on file). The majority of magrolimab-associated toxicities observed to date have been transient and manageable.

Anemia is an on-target toxicity and typically characterized as a 1–2 g/dL fall in hemoglobin during the first 1 to 2 weeks of treatment. Use of a low dose priming and maintenance dose mitigates this hematological effects of magrolimab. Affected patients develop a compensatory reticulocytosis in the ensuing weeks. The mechanism of anemia is described in Section 1.2.1. Similar treatment-related effects on neutrophils and platelets have not been observed. Even in patients with R/R AML or NHL patients with limited bone marrow reserves, magrolimab has demonstrated an acceptable benefit-risk ratio. Supportive care with RBC and platelet transfusions, when required, have successfully been administered in

patients without complications.

The IRRs have been observed, most commonly during the initial 2 study treatments. The most frequently reported signs and symptoms of IRR associated with magrolimab included chills, pyrexia, back pain, nausea, headache, vomiting, and dyspnea.

Hemagglutination or clumping of RBCs on the peripheral blood smear has also been observed, typically after the initial priming or first maintenance dose of drug. Although common, it is generally transient and it not been consistently correlated with clinical symptoms or sequelae.

As of 24 July 2019, approximately 124 patients have received at least 1 dose of magrolimab in this NHL 5F9003 study. The most frequent adverse events (AEs) related to any study intervention (magrolimab and/or rituximab and/or gemcitabine and/or oxaliplatin) were IRR, chills, anemia, fatigue, headache, pyrexia, nausea, vomiting, dyspnea, thrombocytopenia, and neutropenia, events that are consistent with the safety profile of each study drug component.

For the most up-to-date information, refer to the magrolimab IB.

1.2.2.2. Summary of Magrolimab Clinical Pharmacology

A summary of the clinical pharmacokinetic (PK) data from human clinical trials with magrolimab is presented in the most recent magrolimab IB.

Overall, the data indicated nonlinearity in the PK profiles over the dose range 0.3 to 30 mg/kg – the apparent terminal half-life ($t_{1/2}$) was higher at the higher doses of 10 to 30 mg/kg compared to the lower doses indicating potential target mediated drug disposition. Drug exposures were dose proportional at doses ≥10 mg/kg, and a typical antibody-like profile with extended half-life was seen at these doses.

PK analysis showed a large difference in maximum serum concentration (C_{max})

between the first and second doses at the dose of 1 mg/kg, indicating possible time-varying PK at this dose. After the first dose of 1 mg/kg, the C_{max} was approximately 0.575 mcg/mL, whereas the C_{max} after the second dose of 1 mg/kg was 10.6 mcg/mL (approximately 15-fold higher). On subsequent dosing, there were no further changes in the PK at this dose level. Furthermore, at higher doses (3, 10, 20, and 30 mg/kg), the PK profile was similar after the second and fifth doses, suggesting that the time variant PK only occurred at 1 mg/kg between the first and second weekly doses. All pre-first-dose concentrations were below the limit of quantitation (BLQ), indicating that the assay was specific to magrolimab. The mean C_{max} after the 1-mg/kg priming dose was 0.7 mcg/mL. This concentration was associated with near-maximal receptor occupancy (RO) on RBCs (see magrolimab IB v7.0), indicating that this was an appropriate priming dose (Sikic 2016). Consistent with this profile, minimal accumulation in PK (< 2-fold) after multiple maintenance doses was seen at all doses between Weeks 2 and 5.

Binding of magrolimab to the CD47 receptor at various time points after the start of the dosing regimen was measured on circulating red and white blood cells (WBCs) using two RO assays. The RO assay data indicated that at a priming dose of 1 mg/kg, full RO was achieved before the end of first week on RBCs, indicating that this is an appropriate priming dose.

Anti-drug antibody (ADA) data have been evaluated. When ADA values were positive, titer values indicated that these ADAs were low in strength. A visual comparison of the PK of ADA+ and ADA- patients indicated lack of impact of ADA on the PK profile. Additional information can be found in the magrolimab IB.

1.2.2.3. Summary of Magrolimab Clinical Efficacy

Magrolimab as monotherapy at ascending dose levels (Study SCI-CD47-001) in patients with solid tumor showed two patients with objective responses. Study SCI-CD47-002 demonstrated limited efficacy of magrolimab as single agent in patients with AML.

Studies 5F9004 (solid tumor/CRC Phase 1b in combination with cetuximab) and 5F9006 (solid tumor/ovarian cancer Phase 1b in combination with avelumab) are ongoing and have demonstrated limited signs of activity.

Studies 5F9003 (current study) and 5F9005 (AML/MDS [myelodysplastic syndrome]) Phase 1b/2 in combination with azacitidine [AZA]) have demonstrated signs of clinical activity and are ongoing.

For additional information, refer to the magrolimab IB.

1.3. Rituximab

Rituxan®/MabThera® (rituximab), manufactured by Roche/Genentech, is a chimeric murine/human IgG1 kappa mAb that targets CD20. Its MOAs are thought to be antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and induction of apoptosis after binding to the CD20 antigen on the cell surface. The biological effect is manifested by B-cell depletion in peripheral blood, lymph nodes, and bone marrow. Rituximab is the first commercially available mAb for the treatment of lymphoma and is currently approved for several NHL indications including low-grade indolent lymphoma, chronic lymphocytic leukemia, and DLBCL. Rituximab is widely used in frontline and salvage regimens in B-cell NHL, either alone or in combination with chemotherapy. The estimated median terminal elimination half-life is 22 days (range 6.1 to 52 days), based on a population PK analysis of data from 298 NHL patients who received rituximab once weekly or once every 3 weeks (Appendix A).

1.4. Gemcitabine and Oxaliplatin Combination

GEMZAR® (gemcitabine HCl) is a nucleoside metabolic inhibitor that exhibits antitumor activity (Appendix F). Gemcitabine HCl is 2´-deoxy-2´, 2´-difluorocytidine monohydrochloride (β-isomer). The half-life of gemcitabine ranges from 1.7 to 19.4 hours. ELOXATIN® (oxaliplatin for injection and oxaliplatin injection) is an antineoplastic agent with the molecular formula $C_8H_{14}N_2O_4Pt$ and the chemical name of cis-[(1 R,2 R)-1,2 cyclohexanediamine-N,N'] [oxalato(2-)- O,O'] platinum (Appendix G). Oxaliplatin is an organoplatinum complex in which the platinum atom is complexed with 1,2-diaminocyclohexane and with an oxalate ligand as a leaving group. Combination therapy of gemcitabine and oxaliplatin (chemotherapy) with rituximab is a standard treatment for second-line and salvage therapy in DLBCL. The half-life of oxaliplatin is reported to have multiple phases, characterized by 2 relatively short distribution phases ($t_{1/2}\alpha$; 0.43 hours; and $t_{1/2}\beta$; 16.8 hours) and a long terminal elimination phase ($t_{1/2}\gamma$; 391 hours).

1.5. Correlative Studies Background

Blockade of the CD47-SIRPα signaling axis on tumor cells by a monoclonal blocking anti-CD47 antibody leads to tumor elimination by activation of both the innate and adaptive immune system. Anti-CD47 antibody-mediated tumor elimination by the innate immune system occurs through phagocytic elimination of tumor cells by macrophage and other phagocytes. In nonclinical studies, anti-CD47 antibody-mediated tumor cell phagocytosis has been demonstrated to occur through both antitumorigenic M1 and protumorigenic M2 macrophages (Zhang 2016). In addition, in vivo treatment of human xenograft tumors with an anti-CD47 antibody demonstrated increased M1 intratumoral macrophages (Zhang 2016), suggesting that an anti-CD47 antibody can also shift the phenotype of macrophages from the M2 toward the M1 phenotype. Since the recruitment of macrophage effectors is a key mechanism for antitumor activity by anti-CD47 antibody, the characterization of macrophage tumor infiltration pre- and post-treatment in patients treated with anti-CD47 antibody may provide insights into patient and cancer subtypes and macrophage biomarkers that will enrich for antitumor efficacy.

In addition to modulating the innate immune system, anti-CD47 antibody therapy also activates the adaptive immune system towards an antitumor response.

Phagocytosis of tumor cells by macrophages and/or dendritic cells lead to cross-presentation of tumor antigens to T cells, enabling a T-cell antitumor response (Tseng 2013; Liu 2015a). In one nonclinical study, anti-CD47 antibody mediated a specific CD8 T-cell antitumor response without proliferation of regulatory T cells (which are generally thought to be tumor promoting; Tseng 2013). Currently, there is intense interest in investigating the relationship between T-cell subsets that infiltrate the tumor and clinical response with the use of immune-oncology therapeutics. Given the role of anti-CD47 antibody in mediating an antitumor T-cell response, the clinical investigation of the contribution of T-cell effectors to anti-CD47 antibody-mediated efficacy is important to select for patients and tumor subtypes that respond to therapy.

1.6. Study Rationale and Risk-Benefit

1.6.1. Antibody Combination (Magrolimab + Rituximab)

B-cell NHL patients with both indolent lymphomas and DLBCL who have relapsed or are refractory to treatment regimens containing rituximab have limited options for effective treatment. Specific indolent lymphomas, particularly FL, are deemed incurable, as described by frequent patterns of relapse during several lines of therapy. While overall survival (OS) for FL can be more than 10 years, approximately 15% to 20% of patients with newly diagnosed FL have rapidly evolving, progressive disease that results in death within 2 to 3 years (Swenson 2005). Patients suffering from indolent lymphoma with high-risk disease features who have early disease recurrence after treatment with rituximab, are refractory to rituximab containing therapies, or are ineligible for more aggressive therapies represent an unmet medical need. Of patients with DLBCL, 30% to 40% relapse after first-line therapy and 10% experience refractory disease (Vaidya 2014; Morrison 2015). For patients with chemosensitive disease, the standard treatment

for R/R DLBCL is salvage chemotherapy followed by autologous hematopoietic cell transplantation (Philip 1995). Patients with DLBCL who are refractory to frontline therapy, relapse, or are refractory to second line salvage regimens or autologous hematopoietic cell transplantation have an extremely poor prognosis (Gisselbrecht 2010; Crump 2014; Van Den Neste 2016). In these settings, there is no standard treatment. Thus, R/R DLBCL represents a significant unmet need.

Magrolimab in combination with rituximab has been shown to have synergistic antitumor activity in nonclinical B-cell NHL models and provided a rationale for the clinical investigation of this combination in B-cell NHL patients. To date, the safety profile of magrolimab in combination with rituximab has been shown tolerable. Anemia, neutropenia, febrile neutropenia, leucopenia, and thrombocytopenia are adverse drug reactions associated with magrolimab and rituximab. Monitoring and management guideline for these potentially overlapping toxicities are provided in Section 6.2.

Given the nonclinical and initial clinical evidence of activity for combination therapy with an anti-CD47 antibody and rituximab in both indolent lymphomas and DLBCL, the individual safety profiles of both magrolimab and rituximab to date showing tolerability, and the significant unmet medical need for these patient populations, the clinical combination therapy proposed for investigation in this trial has an acceptable risk-benefit profile for the patients proposed for enrollment.

For reference safety information and guidance for the Investigator, refer to the current magrolimab IB.

1.6.2. Rationale for Change of Study Design

The Clinical Trial Steering Committee (CTSC) elected to evaluate an additional Phase 2 dose level (DLBCL Phase 2 Cohort 4; Amendment 9) based on emerging clinical data as well as the aggregate safety, efficacy, PK, and pharmacodynamic (PD) data obtained in the completed Phase 1b/2 portions of this study. The principal aim of Amendment 9 is to broaden the therapeutic option to individuals with

R/R DLBCL following multiple lines of therapy. The tumor types eligible for enrollment have been narrowed to R/R de novo or transformed DLBCL, not otherwise specified, to limit the heterogeneity of the study population. Magrolimab dosing schedule has been modified to align with other magrolimab trials (e.g., removal of Cycle 1 Day 11) and for patient convenience (e.g., extend dosing to every 4 weeks (Q4W) for a subset of patients). The order of drug administration has also been changed on Cycle 1 Day 8 (e.g., magrolimab first followed by rituximab) to potentially augment antitumor activity. Laboratory, PK, PD, and tumor response assessments have been reduced based on the aggregate of safety, PK, and PD data generated during the study to date and to improve patient convenience. Peripheral blood and tumor immunophenotyping studies have been added as research assessments to help better understand the MOA of magrolimab combinations.

1.6.3. Chemotherapy Combination (Magrolimab + R-GemOx)

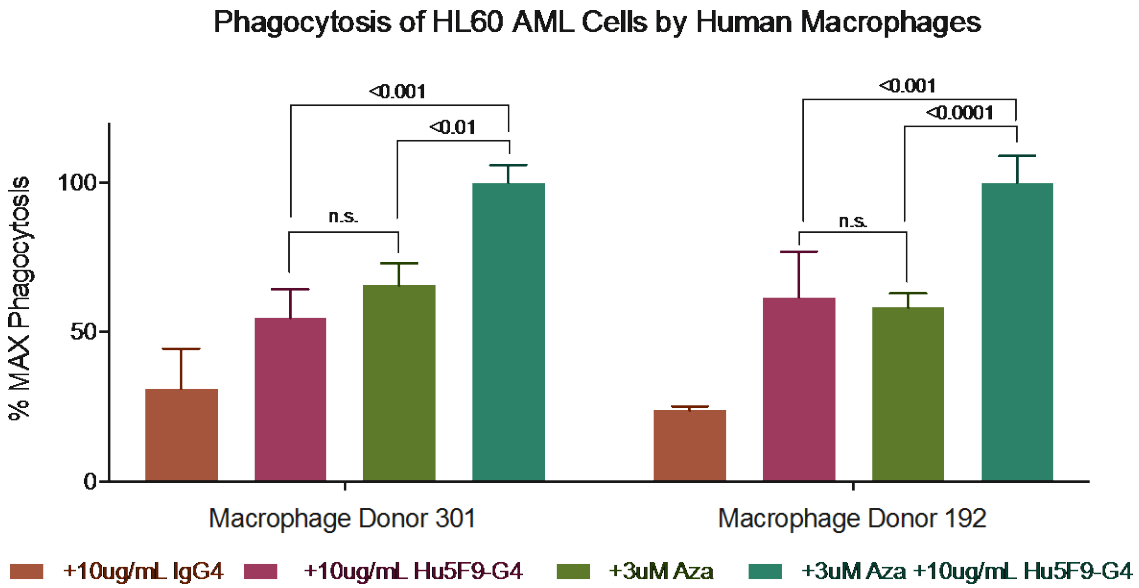
1.6.3.1. Rationale for Study Design and Risk-Benefit

The DLBCL patients who are ineligible for high-dose chemotherapy salvage regimens and ASCT have a poor prognosis (Mounier 2013) and treatment options are limited. No true standard of care exists in this population, with patients often receiving rituximab-chemotherapy regimens such as R-GemOx or palliative care (Mounier 2013, Merchionne 2014). However, significant clinical benefit with R-GemOx and other rituximab/salvage chemotherapies is limited due lack of durable responses. The addition of magrolimab may augment antitumor activity of R-GemOx based on the previously described clinical data and the nonclinical rationale described below.

Chemotherapy combinations have the potential to augment efficacy of anti-CD47 antibodies through induction of pro-phagocytic signals leading to synergistic tumor cell phagocytosis by anti-CD47 antibodies. Certain chemotherapies have been shown to upregulate calreticulin, a major pro-phagocytic signal expressed on tumors (Obeid 2007). For example, AZA, an anti-cancer agent nucleoside analog, has been shown to upregulate calreticulin (Boasman 2017) leading to an enhanced

therapeutic response when combined with magrolimab. Magrolimab, when combined with AZA, led to significantly increased phagocytosis of cancer cells in vitro compared with either agent alone (Figure 1-1).

Figure 1-1 Combination Treatment of AML Cells with AZA and Magrolimab Enhanced Phagocytic Elimination by Human Macrophages In Vitro



Source: Study FSI-2017-001.
Abbreviations: AML = acute myeloid leukemia; AZA = azacitidine; Ig = immunoglobulin.

These combined data from another nucleoside analog + magrolimab combination study support the mechanistic rationale of combination of magrolimab with other agents including R-GemOx. In addition, the initial DLBCL efficacy signals observed with magrolimab + rituximab in the current study provide expectation for enhanced activity with the addition of gemcitabine and oxaliplatin. From a safety perspective, the addition of magrolimab to R-GemOx is not anticipated to lead to additional significant toxicities based on the observation that magrolimab has been well-tolerated with rituximab in Phase 1b study.

In the current clinical study, magrolimab has been shown to be well-tolerated in the Phase 1b experience with encouraging preliminary efficacy signals observed in heavily pretreated DLBCL patients, and an acceptable safety profile. Importantly, a 30 mg/kg magrolimab dose was well-tolerated in combination with rituximab without an MTD being reached. This data justifies the use of 30 mg/kg of magrolimab as a

starting dose for the combination with R-GemOx. The addition of magrolimab to R-GemOx therapy may enhance clinical efficacy while maintaining an acceptable risk:benefit profile. In summary, the combination of magrolimab and R-GemOx may be more efficacious in high-dose chemotherapy/ASCT ineligible DLBCL patients who have a high unmet medical need. The addition of magrolimab to R-GemOx is expected to be relatively well- tolerated. Thus, the potential efficacy:safety profile justifies a risk:benefit ratio for the investigation of magrolimab in combination with R-GemOx in ASCT ineligible DLBCL.

1.7. Dose Rationale

1.7.1. Antibody Combination (Magrolimab + Rituximab): Phase 1b Magrolimab

Because CD47 is widely expressed on normal tissues, effective tumor penetration by magrolimab requires a dose regimen that ensures adequate saturation of the internal CD47 receptor sink and achieves effective circulating drug levels. In the Phase 1 trial of magrolimab in solid tumors, maintenance dose concentrations between 10 and 30 mg/kg weekly were associated with circulating magrolimab drug levels that correlated with nonclinical anti-cancer efficacy. The Phase 1b portion of this trial was designed to investigate a 1-mg/kg priming dose followed by weekly maintenance doses of 10, 20, 30, or 45 mg/kg.

Escalating doses of magrolimab were evaluated in combination with 375 mg/m^2 of rituximab (Table 6-1). Based on the aggregate safety, efficacy, PK, and PD data obtained in the Phase 1b portion of the study of patients with NHL, the CTSC determined a recommended Phase 2 dose and schedule (RP2DS) for magrolimab. In summary, the magrolimab RP2DS is as follows: a priming dose of 1 mg/kg followed by maintenance doses of 30 mg/kg; administration will be intravenous (IV) weekly during Cycle 1, and then every 2 weeks (Q2W) starting at Cycle 2. (Refer to Section 3.1.1.1 for additional details on RP2DS selection.)

Patients enrolled in Phase 1b and continuing in study may be transitioned to the RP2DS for magrolimab and the schedule for rituximab administration for Phase 2, as described in Section 6.1.1.2.

Dose Rationale

The following dosing regimen is proposed for further testing in this study: priming (1 mg/kg) on Day 1, followed by doses of 30 mg/kg on Day 8 and every week thereafter for the first 2 cycles, followed by 30 mg/kg Q2W from Cycle 3 Day 1 onwards. Rationale for the proposed dose comes from safety, efficacy, and pharmacokinetic/pharmacodynamic (PKPD) modeling and simulation data obtained from all ongoing and completed clinical trials with magrolimab in patients with solid tumors, NHL, and AML/MDS.

In the first-in-human study of magrolimab SCI-CD47-001 in patients with solid tumors and hematological malignancies, after an initial priming dose of 1 mg/kg on the first day, magrolimab was tested as a monotherapy at weekly doses of up to 45 mg/kg. No significant dose-dependent toxicities were observed across the dose range tested. In studies SCI-CD47-002 and 5F9005, in patients with myeloid malignancies, magrolimab was administered as a monotherapy at doses of up to 30 mg/kg twice weekly and in combination with AZA and at doses of up to 30 mg/kg weekly, respectively. In these studies, no significant dose-dependent toxicity was observed and magrolimab was well-tolerated over the tested dose range. In studies 5F9003 and 5F9004, magrolimab, in combination with rituximab and cetuximab, respectively, was found to be safe and well-tolerated at doses of 45 mg/kg every other week. All doses were found to be safe and well-tolerated, and no MTD was identified in any of the trials (see IB Section 5.3.1). Based on the integrated safety data in multiple oncology populations including the proposed study population, both as a monotherapy and in combination with other tumor-targeted antibodies and chemotherapeutics, the proposed dosing regimen of magrolimab is expected to be safe and well-tolerated in NHL patients.

Exposure-response analysis from available dose-ranging data in NHL patients also supports the proposed dosing regimen. After a priming dose of 1 mg/kg in the first week, maintenance doses in the range of 10–45 mg/kg every week and

30–45 mg/kg Q2W were tested in the Phase 2 portion of the ongoing Phase 1b/2 trial of magrolimab in combination with rituximab in R/R NHL patients (Study 5F9003). Based on data obtained from this study so far, there was no significant difference in efficacy across the dose range tested. For instance, in R/R DLBCL, the objective response rate (ORR) of patients in the combined 30 mg/kg dose arm (N=35) and at 45 mg/kg (n=17) was 34% and 38%, respectively (Advani 2019). The PKPD modeling also indicated lack of relationship between exposure and ORR across the entire dose/concentration range tested in Phase 1 and Phase 2 studies. Also, no relationship was observedbetween concentrations and duration of response (DOR) in responders across thetested dose range. Put together, these results indicated maximal efficacy at 30 mg/kg with no further efficacy benefit at higher doses. In addition, in study 5F9003, maximal CD47 RO was observed at the maintenance dose of 30 mg/kg twice weekly.

In summary, the proposed dose regimen has been shown to be safe and well-tolerated in multiple oncology patient populations, including NHL patients. Based on PKPD modeling, the proposed dose is predicted to result in optimal efficacy in this population. Further increases in dose beyond 30 mg/kg are not predicted to result in increased efficacy.

Please refer to Section 5.3.1 of the most recent version of the magrolimab IB for further information on safety analyses and the magrolimab IND Module 5 and PKPD modeling and simulation report (FSI-2019-014) for the population PKPD analysis that supports this dosing justification.

Rituximab

Rituximab will be administered at the clinically approved dose concentration of 375 mg/m^2 IV. In Phase 1b, rituximab was given in a loading/maintenance dose regimen that included weekly doses of 375 mg/m^2 on Days 8, 15, and 22 during the first cycle, followed by 1 dose of 375 mg/m^2 per cycle for up to 6 total cycles. The dose regimen was selected based on the PK profile of rituximab, as well as evidence that a loading/maintenance regimen enhances efficacy in pretreated NHL patients (Ghielmini 2004).

The rituximab dosing will be changed to Day 1 of Cycles 2 through 6, and Day 1 of every other cycle starting with Cycle 8 and beyond, as outlined in Table 6-1 and Table 6-2. The MOA of magrolimab synergy with rituximab relies on a constant supply of pro-phagocytic signal generated by rituximab's Fc receptor.

1.7.2. Antibody Combination (Magrolimab + Rituximab): Phase 2 Magrolimab

Magrolimab will be administered at a 1 mg/kg priming IV dose on Day 1, followed by weekly maintenance doses of 30 mg/kg during Cycle 1, followed by 30 mg/kg dosing Q2W for Cycle 2+ until disease progression. Refer to Section 3.1.1.3.

Based on emerging clinical data as well as the aggregate safety, efficacy, PK, and PD data obtained in the completed Phase 1b/2 portions of this study, the dosing of the new DLBCL Phase 2 Cohort 4 arm (Amendment 9), is being implemented as follows:

A priming dose of 1 mg/kg followed by maintenance doses of 30 mg/kg; administration will be IV weekly during Cycles 1 and 2, and then Q2W starting at Cycle 3. The order of dose administration on Cycle 1, Day 8 will consist of magrolimab followed by rituximab. Cycle length is 28 days; refer to Section 6.1.1.1 for additional details on magrolimab administration; refer to Section 1.7 for the starting dose rationale.

Please refer to Section 5.3.1 of the most recent version of the magrolimab IB for further information on safety analyses and the magrolimab IND Module 5 and PKPD modeling and simulation report (FSI-2019-014) for the population PKPD analysis that supports this dosing justification.

Rituximab

Rituximab will be administered at the clinically approved dose concentration of 375 mg/m^2 IV weekly starting Day 8 through Cycle 1. Rituximab will then begiven monthly on Day 1 from Cycles 2 through 6, then every other month of Day 1 starting Cycles 6 and beyond until loss of clinical benefit or unacceptable toxicity.

1.7.3. Chemotherapy Combination (Magrolimab + R-GemOx)

R-GemOx is an established treatment regimen for DLBCL with a known toxicity profile when given together in the similar regimen as investigated in this study (Lopez 2008; Mounier 2013).

Magrolimab

In the chemotherapy combination cohort, magrolimab will be first evaluated in dose escalation with R-GemOx. The magrolimab dosing in the dose-escalation cohort will be administered at a 1 mg/kg priming IV dose on Day 1, with a higher maintenance IV dose on Day 8, 11, 15, 22, and 29 in Cycle 1 and weekly maintenance doses through Cycle 2. After Cycle 2, maintenance doses will be Q2W until disease progression. Refer to Table 6-3 for specific dosing regimens for magrolimab in the safety dose-escalation and expansion cohort. The Cycle 1 Day 11 magrolimab loading dose has been eliminated for the Dose-Expansion cohort as of Amendment 9.

Rituximab

Rituximab will be utilized similarly to the dosing schedule determined in the Phase 1b magrolimab + rituximab dose escalation portion of this study. Rituximab will be administered at the approved dose concentration of 375 mg/m^2 IV weekly starting Day 8 through Cycle 1. Rituximab will then be given monthly on Day 1 of each cycle from Cycles 2 through 6 and then Day 1 every other cycle starting at Cycle 8 and continue until disease progression or unacceptable toxicity.

Gemcitabine

Gemcitabine will be administered at 1000 mg/m^2 on Days 11 and 23 of Cycle 1, and subsequently on Day 2 and 15 of Cycles 2 through 4. This dosing regimen is based on a widely utilized dose of 1000 mg/m^2 on a Q2 week schedule for up to 4 months in combination with rituximab and oxaliplatin in ASCT ineligible DLBCL (Mounier 2013). Patients may receive gemcitabine for longer than 4 cycles to receive the total 8 doses if dose delays occur. Gemcitabine is a dministered on days

separate from rtuximab to avoid potential infusion reaction and other toxicities (Lopez 2008).

Oxaliplatin

Oxaliplatin will be administered at 100 mg/m^2 on Days 11 and 23 of Cycle 1, and subsequently on Day 2 and 15 of Cycles 2 through 4. This dosing regimen is based on a widely utilized dose of 100 mg/m^2 on a Q2 week schedule for up to 4 months in combination with rituximab and oxaliplatin in ASCT ineligible DLBCL (Mounier 2013). Patients may receive oxaliplatin for longer than 4 cycles to receive the total 8 doses if dose delays occur. Oxaliplatin is administered on days separate from rituximab to avoid potential infusion reaction and other toxicities.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives and endpoints for the study are outlined below in Table 2-1.

Table 2-1 Study Objectives and Endpoints

PRIMARY	
Objectives	**Endpoints**
• To investigate the safety and tolerability, and to define the RP2DS for magrolimab in combination with rituximab and for magrolimab in combination with R-GemOx • To evaluate the efficacy of magrolimab in combination with rituximab in patients with indolent lymphoma and DLBCL and to evaluate the efficacy of magrolimab in combination with R-GemOx in ASCT ineligible DLBCL as measured by the ORR according to Lugano Classification for lymphomas (Cheson 2014; Table 10-1)	• DLTs (Phase 1b only [in the antibody combination (magrolimab + rituximab) and the chemotherapy combination (magrolimab + R-GemOx) cohorts]) and AEs according to NCI CTCAE, Version 4.03 • ORR as defined by the Investigator according to the Lugano Classification for lymphomas (Table 10-1)
SECONDARY	
Objectives	**Endpoints**
• To evaluate the PK profiles of magrolimab in combination with rituximab and magrolimab in combination with R-GemOx • To evaluate the immunogenicity of magrolimab in combination with rituximab and magrolimab in combination with R-GemOx • To evaluate the efficacy of magrolimab in combination with rituximab in indolent lymphoma and DLBCL and magrolimab in combination with R-GemOx in ASCT ineligible DLBCL as measured by the DOR, PFS, OS, and TTP • To evaluate the efficacy of magrolimab in combination with rituximab in patients with indolent lymphoma and DLBCL and magrolimab in combination with R-GemOx in ASCT ineligible DLBCL as measured by ORR according to LYRIC (Cheson 2016; Table 10-2)	• Concentration versus time measurements for magrolimab in combination with rituximab and for magrolimab in combination with R-GemOx and their PK parameters including C_{max} and AUC • ADA to magrolimab in combination with rituximab and magrolimab in combination with R-GemOx • DOR, PFS, OS, and TTP • ORR as defined by the Investigator according to the LYRIC Criteria for lymphomas (Table 10-2)


CCI


CCI

3. STUDY DESIGN

3.1. Overall Study Design

This trial is an open-label, multicenter, Phase 1b/2 trial investigating the combination of magrolimab + rituximab (antibody combination; Section 3.1.1) and magrolimab + R-GemOx (chemotherapy combination; Section 3.1.2) in R/R B-cell NHL.

3.1.1. Antibody Combination (Magrolimab + Rituximab)

3.1.1.1. Phase 1b Study Design (Magrolimab + Rituximab)

The dose escalation portion of the Phase 1b cohort followed a standard 3 + 3 study design in patients with B-cell NHL received magrolimab and rituximab to investigate a 1-mg/kg magrolimab priming dose followed by weekly maintenance doses of 10, 20, 30, or 45 mg/kg to determine the MTD and to identify the recommended Phase 2 dose and schedule (RP2DS) for magrolimab in combination with rituximab.

Rituximab was administered by IV infusion at the clinically approved dose of 375 mg/m^2. Rituximab was given in a regimen that includes weekly doses on Days 8, 15, and 22 during Cycle 1, followed by 1 dose on Day 1 of Cycles 2 through 6, and Day 1 of every other cycle thereafter. During Cycle 1, Weeks 2 through 4, and for Cycles 2 through 6, magrolimab and rituximab were administered on the same day. On days on which both rituximab and magrolimab were given for Cycle 1 Day 8 and beyond, rituximab was given first. Magrolimab was given at least 1 hour after the rituximab infusion was completed.

Dose escalation of magrolimab proceeded through the designated dose levels, as shown in Table 6-1. Decisions related to dose escalation were based on the first 4 weeks of treatment in the current cohort, referred to as the “Dose-Limiting Toxicity (DLT) Assessment Period,” in conjunction with ongoing assessments for patients on prior cohorts who continued therapy beyond 4 weeks. Dose Level 3 exploration was based on ongoing PK evaluation and clinical data review, and as decided by the CTSC. Ten patients were added to Dose Level 3 (that was

previously demonstrated to be safe) for the purpose of confirming the tolerability of magrolimab and to provide additional PK data to assist in the selection of an RP2DS. The CTSC subsequently recommended to open-dose Level 4 to evaluate magrolimab at 45 mg/kg in Phase 1b.

Phase 1b for magrolimab + rituximab has enrolled 29 total patients (3 in Level 1, 6 in Level 2, 13 in Level 3, 7 in Level 4) (data on file).
Dose escalation and cohort expansion decisions were reviewed and approved by the CTSC.

The rationales for the study and for the dose(s) are provided in Section 1.6 and Section 1.7, respectively. Based on review of safety, efficacy, and PK data available from Phase 1b (as outlined in Section 1.6.2), the CTSC determined that the Phase 1b dose-escalation phase of the trial reached sufficient evidence to determine a magrolimab RP2DS of a 1 mg/kg priming dose, followed by 30 mg/kg IV weekly during Cycle 1, and then Q2W (cycle length is 28 days).

Dose-Limiting Toxicity Evaluation (Magrolimab + Rituximab)

Dose escalation decisions were made by the CTSC based on the first 4 weeks of treatment for each patient, referred to as the “Dose-limiting Toxicity (DLT) Assessment Period.” The first patient in each dose cohort completed at least 1-week of treatment before additional patients were enrolled in the cohort. The third patient in a cohort completed the DLT Assessment Period prior to escalating to the next dose level.

DLT-evaluable Patients (Magrolimab + Rituximab)

Patients assigned to a particular dose cohort in Phase 1b were considered evaluable for assessment of DLT if EITHER of the following criteria were met during the DLT assessment period:

- The patient experienced a DLT.
- The patient completed at least 3 infusions of magrolimab and 2 infusions of rituximab.

For the Phase 1b part of the study, patients who withdrew before completing the 4-week DLT assessment period for reasons other than a DLT, or who do not fulfill either of the criteria above, were not evaluable for assessment of DLT for dose review decisions and were replaced in the cohort.

Definition of DLT (Magrolimab + Rituximab)

Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03 (Appendix B). A DLT was defined as any Grade 3 or greater AE that is assessed as related to study drug (magrolimab and/or rituximab) that occurs during the 4-week DLT observation period. DLTs applied only to patients in the Phase 1b part of the study for the magrolimab + rituximab cohort.

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

- Grade 3 anemia, however, Grade 3 hemolytic anemia that is medically significant, requires hospitalization or prolongation of existing hospitalization, is disabling, or limits self-care activities of daily life (ADL) is considered a DLT.
- Grade 3 indirect/unconjugated hyperbilirubinemia that resolves to ≤ Grade 2 with supportive care within 1 week and is not associated with other clinically significant consequences.
- Isolated Grade 3 electrolyte abnormalities that resolve to ≤ Grade 2 with supportive care within 1 week and are not associated with other clinically significant consequences.
- Grade 3 elevation in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase that resolves to ≤ Grade 2 with supportive care within 1 week and is not associated with other clinically significant consequences.
- Transient Grade 3 nausea, vomiting, diarrhea, local reactions, influenza-like symptoms, myalgias, fever, headache, or acute pain that resolves to

≤ Grade 2 within ≤ 72 hours with supportive care.

- Grade 3 fatigue that resolves to ≤ Grade 2 within 2 weeks on study
- Grade 3 magrolimab or rituximab-related infusion reactions in the absence of an optimal pretreatment regimen, which is defined as acetaminophen or a comparable non-steroidal anti-inflammatory agent, plus an antihistamine and corticosteroids.
- Grade 3 tumor lysis syndrome or related electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia) that resolve to ≤ Grade 2 within 7 days
- Grade 3 or 4 lymphopenia
- Grade 3 infusion reactions attributed to rituximab; an infusion reaction can only be attributed to rituximab alone if the infusion reaction occurs after the start of rituximab infusion, but prior to magrolimab infusion, on days where rituximab and magrolimab are both dosed

3.1.1.2. Recommended Phase 2 Dose and Schedule (Magrolimab + Rituximab)

As noted in Section 1.6.2 and Section 3.1.1 the CTSC determined a RP2DS for magrolimab based on data obtained in the Phase 1b portion of this study. Based on emerging data, the CTSC may select additional Phase 2 doses and schedules for evaluation.

3.1.1.3. Phase 2 Study Design (Magrolimab + Rituximab)

The Phase 2 part of the study will explore the combination of magrolimab + rituximab at the RP2DS determined from Phase 1b antibody combination (magrolimab + rituximab) in 2 separate cohorts: 1) patients with indolent lymphoma (to include FL and marginal zone lymphoma), and 2) patients with DLBCL. For the Phase 2 part of the study, dosing will be as described in Section 6.1.1.1 and Section 6.1.1.2. Treatment for patients in the 2 cohorts will be conducted according to an initial two-stage design. After 14 patients in each arm have been enrolled, an efficacy futility analysis will be performed. Patients who do not complete at least 8 weeks on study may be replaced. If ≥ 3 patients out of 14 achieve an ORR in

either cohort, enrollment may continue in the respective cohort. For any interim analysis point, accrual in either arm may be opened earlier by the CTSC at any point at which sufficient anti-cancer activity is observed.

For the DLBCL cohort (Phase 2 Cohorts 1 to 3), if the initial stage of clinical activity is met (in the first evaluable 14 patients), the CTSC will convene to review and approve proceeding with subsequent accrual of 40 efficacy-evaluable patients of either or both DLBCL and indolent lymphoma cohorts or to terminate the study according to the pre-specified stopping rules described in Section 11.4.1.

Per Amendment 9, the inclusion criteria were modified for DLBCL patients, and as such, this DLBCL cohort under the new inclusion criteria may be expanded to 100 total patients for potential registrational approval. After the first 20 efficacy-evaluable patients, an efficacy analysis will be conducted by the CTSC, with subsequent determination to enroll the full 100 patients or to stop enrollment. Enrollment may proceed if an ORR of 20% (4/20 patients) or higher is achieved with the 20 efficacy-evaluable patient analysis.

For the indolent lymphoma cohort, if the initial stage of clinical activity is met (in the first evaluable 20 patients), the CTSC will convene to review and approve proceeding with subsequent accrual of at least 24 efficacy-evaluable patients. After this interim analysis in at least 24 patients, the CTSC will review and may proceed with subsequent enrollment up to approximately 94 evaluable patients in the indolent lymphoma cohort.

The CTSC may also approve further enrollment and exploration of additional alternate Phase 2 doses to evaluate 14 additional patients given the heterogeneity of DLBCL and indolent lymphoma patients or to explore alternative dose regimens that may enhance efficacy. If alternative dosing regimens in Phase 2 are explored, then this futility analysis in an additional 14 patients will also be applied and further enrollment in either DLBCL or indolent lymphoma will occur as described above.

As noted in Section 3.1.1, the CTSC has determined the RP2DS for

magrolimab based on data obtained in the Phase 1b antibody combination (magrolimab + rituximab) portion of the study. Refer to Section 6.1 for details of study drug administration.

3.1.2. Chemotherapy Combination (Magrolimab + R-GemOx)

The combination of magrolimab + R-GemOx will be explored in a Phase 1b design with an initial safety dose-escalation phase (with dose de-escalation if necessary) followed by an expansion phase in high-dose chemotherapy/ASCT ineligible patients.

Table 7-2 outlines post-treatment assessments for the safety dose-escalation and expansion phases of the magrolimab + R-GemOx cohort. PK assessments are outlined in Table 7-3 and correlative studies time points are outlined in Table 7-4. The Schedule of Assessments (SOA) for the chemotherapy combination (magrolimab + R-GemOx) is provided in Table 7-5.

3.1.2.1. Phase 1b Safety Dose-Escalation Phase (Magrolimab + R-GemOx)

In the Phase 1b safety dose-escalation phase, a dose escalation of magrolimab in combination with R-GemOx will be investigated to determine the MTD, if one exists, and to identify a recommended magrolimab + R-GemOx dose for use in the expansion cohort.

Three to 6 patients will be enrolled in each dose cohort. If none of the first 3 patients experienced a DLT, dose escalation can proceed to the next higher dose cohort or the cohort can be expanded. If 1 of the first 3 patients experience a DLT, the cohort will be expanded to 6 patients. If ≥ 34% of patients in a dose level experience a DLT at any time, the MTD dose level will be exceeded in that cohort, and dose escalation is to be halted. Additional patients can be treated at a lower dose level. The selected dose for the expansion phase must not exceed a 34% DLT rate in at least 6 patients treated.

Patients will receive magrolimab + R-GemOx according to the dose schedule

outlined in Section 6.1.2, Table 6-3. The Phase 1b dosing will start at dose level 1, using a 1 mg/kg magrolimab priming and 30 mg/kg maintenance doses in combination with standard dose R-GemOx. If this cohort is deemed to be safe, dosing will proceed to dose level 2 using a 45 mg/kg magrolimab maintenance dose. If the MTD is exceeded in cohort 1, then dose de-escalation will occur and the dose level -1 will be enrolled using a 1 mg/kg magrolimab priming and 20 mg/kg maintenance dose in combination with standard dose R-GemOx. Dose de-escalation of magrolimab to a 10 mg/kg maintenance dose may be further explored in another 6 patients if the 20 mg/kg maintenance dose level exceeds the MTD. The CTSC can decide to explore higher doses of magrolimab (beyond dose level 2) up to a 50% higher dose than the prior dose level in accordance with the modified 3+3 design and if the lower dose level is deemed to be safe.

The first patient in each dose level is required to complete at least 9 days of treatment before additional patients are enrolled in the cohort. Subsequent patients may be simultaneously enrolled. The third patient in a cohort must complete the DLT Assessment Period before escalating to the next dose level. The Sponsor may decide whether a fourth patient can be enrolled to the same cohort before the first three patients complete the DLT Assessment Period, to have an extra patient in case one of the three earlier patients are not evaluable for DLT or if there is a DLT within the cohort requiring cohort expansion.

The magrolimab dose in combination with R-GemOx used in the expansion phase will be determined by the CTSC based on safety and clinical data. The CTSC may decide to expand any safety dose-escalation cohort to 10 additional patients to any magrolimab dose level combination that is deemed to be safe to collect additional safety, PK, or clinical data. Selection of the recommended dose of magrolimab + R-GemOx for the expansion phase may or may not include the Day 11 magrolimab dose, as determined by the CTSC.

Dose-Limiting Toxicity Evaluation (Magrolimab + R-GemOx)

Safety, tolerability, and dose de-escalation decisions will be made by the CTSC

based on the first 5 weeks of treatment for each patient in the safety dose escalation magrolimab + R-GemOx cohort. Six patients will be initially enrolled, with dose de-escalation cohorts of magrolimab possible based on safety data. The DLT evaluation period will begin starting Week 2 through Week 5. AEs after initiation of the 1 mg/kg magrolimab priming dose on Day 1 and before initiation of gemcitabine and oxaliplatin on Day 11 will not be evaluable as DLTs. The safety dose-escalation cohort is designed to investigate the safety and tolerability of magrolimab and rituximab in combination with gemcitabine and oxaliplatin; therefore, DLTs are evaluated in patients that receive gemcitabine and/or oxaliplatin in addition to magrolimab and rituximab.

DLT-evaluable Patients (Magrolimab + R-GemOx)

Patients enrolled in the safety dose-escalation part of the Phase 1b magrolimab + R-GemOx cohort are considered evaluable for assessment of DLT if EITHER of the following criteria are met during the DLT assessment period:

- The patient experienced a DLT at any time after initiation of the first infusion of magrolimab, rituximab, and gemcitabine or oxaliplatin.
- The patient completed at least 3 infusions of magrolimab, 2 infusions of rituximab, and 1 infusion of gemcitabine and oxaliplatin.

For the safety dose-escalation cohort, patients who withdraw before completing the 5-week DLT assessment period for reasons other than a DLT or who do not fulfill either of the criteria above are not evaluable for assessment of DLT for safety review decisions and will be replaced in the cohort.

Definition of DLT (Magrolimab + R-GemOx)

Toxicities are graded according to the NCI CTCAE, Version 4.03 (Appendix B).
A DLT in this magrolimab + R-GemOx cohort is defined by the criteria listed above in Section 3.1.1.1 with the additional definitions listed below:

- ≥ Grade 4 hematologic toxicity that does not resolve to ≤ Grade 2 and delays initiation of cycle 2 by more than 14 days.
- ≥ Grade 4 febrile neutropenia or associated infections

- ≥ Grade 4 non-hematologic toxicity that does not resolve or decrease to ≤ Grade 2 within 1 week.
- ≥ Grade 4 IRR
- Recurrent ≥ Grade 3 magrolimab, rituximab, gemcitabine, or oxaliplatin IRR despite optimal pretreatment regimen, which is defined as acetaminophen or a comparable non-steroid anti-inflammatory agent, plus an antihistamine and corticosteroids. In addition to the above, optimal pretreatment regimen includes antiemetic pretreatment for gemcitabine and/or oxaliplatin IRRs.

3.1.2.2. Phase 1b Expansion Phase (Magrolimab + R-GemOx)

After the safety dose-escalation phase is completed, the dose regimen of magrolimab + R-GemOx that is well-tolerated and recommended by the CTSC will be utilized in treating 20 patients in an expansion phase to evaluate efficacy of the combination. Table 6-3 (provided in Section 6.1.2) outlines the expansion phase dosing regimen and schedule. For the expansion phase, patients may be enrolled simultaneously without an observation time between patients.

3.2. Clinical Trial Steering Committee

The CTSC will oversee the conduct of the clinical trial. A representative from the Sponsor, usually the Study Medical Monitor or designee, will chair the CTSC. The CTSC will have representation from each participating site in the study. The CTSC will review safety and efficacy data generated during the trial and make decisions about patient recruitment, trial management, initiation of protocol specific amendments, expansion of cohorts, using higher or lower dose levels, defining any new dose cohorts, identification of the RP2DS, and interim efficacy analysis decisions. The CTSC will meet at a minimum at the completion of each dosing cohort during dose-escalation phase of the trial, at any protocol-specified formal interim analyses, and when emergent critical safety data are reported. The composition, structure, and function of the CTSC are defined in the CTSC Charter.

3.3. Data Monitoring Committee

Data Monitoring Committee functions for this trial will be performed by the CTSC, as defined and described in Section 3.2.

3.4. Number of Sites

Approximately 20 sites located in the US, United Kingdom (UK), and Australia will be included in this trial. Additional sites may be included based on enrollment and study timelines.

3.5. Estimated Study Duration and End of Study

Individual patient participation will include screening/enrollment, treatment, and follow-up. It is anticipated that this study will take approximately 42 months for screening/enrollment and treatment of all patients.

4. PATIENT SELECTION AND ENROLLMENT

4.1. Study Entry Criteria

4.1.1. Inclusion Criteria

1. Adults ≥ 18 years
2. Antibody combination (magrolimab + rituximab) Phase 1b cohort only: B-cell NHL expressing CD20 by immunohistochemistry (IHC) or flow cytometry, relapsed or refractory to at least 2 prior lines of therapy.
3. DLBCL chemotherapy combination (magrolimab + R-GemOx) Phase 1b safety dose-escalation and expansion cohorts:
   a. Histologically confirmed de novo or transformed DLBCL relapsed or refractory to 1 to 3 prior lines of therapy who are not candidates for high-dose chemotherapy and ASCT. Patients relapsed after ASCT are allowed.
   b. At least 1 prior therapy must have included a CD20-targeted therapy.
   c. Primary refractory patients are excluded as defined by failure to achieve a PR or CR to frontline therapy or progression within 3 months of completing treatment.
   d. The 1 to 3 prior lines of therapy requirement is only applicable for treatment regimens for DLBCL and not for prior lymphomas in the case of transformed DLBCL.

4. For the DLBCL antibody combination (magrolimab + rituximab) Phase 2 Cohort 4, de novo or transformed DLBCL, not otherwise specified, according to the World Health Organization 2016 classification of lymphoid neoplasms (Swerdlow 2016) expressing CD20 by IHC or flow cytometry, that is relapsed orrefractory to at least 2 prior lines of therapy containing and anti-CD20 therapy. Prior autologous hematopoietic cell transplantation is permitted.
5. Indolent lymphoma Phase 2 Cohort: Histologically confirmed marginal zone or FL (Grade 1 to 3a) expressing CD20 by IHC or flow cytometry, relapsed or refractory to at least 2 prior lines of therapy.
6. Eastern Cooperative Oncology Group (ECOG) score 0 to 2
7. Disease that is measurable or assessable for response per Lugano Classification for lymphomas (Cheson 2014; Table 10-1)
8. Laboratory measurements, blood counts:
   - Hemoglobin must be $\geq$ 9 g/dL within 24 hours prior to the first 2 doses of magrolimab infusion. NOTE: Transfusions are allowed to meet hemoglobin eligibility (see Section 6.2.1.3 for anemia management)
   - Absolute neutrophil count (ANC) ≥ 1.0 × 10^9/mL
   - For the antibody combination (magrolimab + rituximab) Phase 1b and Phase 2 cohorts: Platelets ≥ 50 × 10^9/mL
   - For the Phase 1b chemotherapy combination (magrolimab + R-GemOx) safety dose-escalation and expansion cohorts only, platelets ≥ 100 × 10^9/mL
9. Laboratory measurements, hepatic function:
   - AST/ALT < 5 × upper limit of normal (ULN)
   - Bilirubin ≤ 1.5 × or 3.0 × ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or a genetic equivalent
10. Laboratory measurements, renal function:
    - Serum creatinine ≤ 1.5 × ULN or calculated GFR > 40 mL/min/1.73 m^2
11. Women of childbearing potential (WOCBP) must not be nursing or planning to be pregnant and must have a negative urine or serum pregnancy test within 30 days before enrollment and within 72 hours before the first administration of magrolimab.
12. WOCBP must be willing to use at least 1 highly effective method of contraception during the study and continue for 4 months after the last dose of magrolimab and 12 months after the last dose of rituximab
13. Male patients who are sexually active with a WOCBP and who have not had vasectomies must be willing to use a barrier method of contraception and refrain from sperm donation during the study and for 4 months after the last dose of magrolimab and 12 months after the last dose of rituximab. If the partner is pregnant, male patients must use barrier method contraception (condom) during the study and for 4 months after the last dose of magrolimab and until there is a pregnancy outcome (whichever is applicable) to prevent fetal exposure to study drugs.
14. Patient has provided informed consent

15. Must be willing and able to comply with clinic visits and procedures outlined in the study protocol
16. DLBCL chemotherapy combination (magrolimab + R-GemOx) Phase 1b safety dose-escalation and expansion cohorts and Phase 2 antibody combination (magrolimab + rituximab) indolent lymphoma and DLBCL cohorts: Willing to consent to 1 mandatory pretreatment and 1 on-treatment tumor biopsy, unless determined to not be feasible by the Investigator (Reasons include, but are not limited to, lack of accessible tumor tissue to biopsy and patient safety issues.)
17. CAR-T naïve or CAR-T ineligible patients and otherwise meet other inclusion/exclusion criteria may enroll. Patients who relapse following CAR-T therapy are not eligible.

4.1.2. Exclusion Criteria

1. Patients with active brain metastases (patients with stable treated central nervous system [CNS] lesions who are off corticosteroid therapy for at least 3 weeks are not considered active)
2. Prior allogeneic stem cell transplant
3. Prior anti-cancer therapy including chemotherapy, hormonal therapy, and investigational agents within 3 weeks or within at least 4 half-lives prior to magrolimab dosing (up to a maximum of 4 weeks), whichever is longer. NOTE: Low dose steroids (oral prednisone or equivalent ≤ 20 mg per day), localized non-CNS radiotherapy, previous hormonal therapy with LHRH agonists for prostate cancer, and treatment with bisphosphonates and RANKL inhibitors are not criteria for exclusion.
4. Known active or chronic hepatitis B or C infection or HIV.
5. RBC transfusion dependence, defined as requiring more than 2 units of RBC transfusions during the 4-week period prior to screening. RBC transfusions are permitted during screening and prior to enrollment to meet the hemoglobin inclusion criteria.
6. History of hemolytic anemia or Evans syndrome in the last 3 months.
7. Positive IgG component of the direct antiglobulin test (DAT).
8. Prior treatment with CD47 or SIRPα-targeting agents.
9. Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancy for which patients are not on active anti-cancer therapy, as defined in Exclusion Criterion 3.
10. Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients of rituximab listed in Appendix A.
11. Significant medical diseases or 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, severely immunocompromised state, and congestive heart failure NYHA Class II-IV.

12. History of psychiatric illness or substance abuse likely to interfere with ability to comply with protocol requirements or give informed consent
13. Pregnancy or active breastfeeding
14. Additional exclusion criteria for DLBCL chemotherapy combination (magrolimab + R-GemOx) Phase 1b safety dose-escalation and expansion cohorts only:
    a. Undergone ASCT within a period of ≤ 3 months before signing informed consent
    b. Prior treatment with gemcitabine and oxaliplatin. However, patients who relapse ≥ 12 months after treatment with a gemcitabine and oxaliplatin-containing regimen are allowed.
    c. Known hypersensitivity to gemcitabine, oxaliplatin, or other platinum compounds
    d. Intolerance of gemcitabine, oxaliplatin, and/or rituximab as monotherapy or in combination due to unacceptable toxicities as determined by the treating Investigator

4.2. Contraception Requirements

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

Female patients of childbearing potential who have a negative serum or urine pregnancy test before enrollment must agree to use one of the following highly effective forms of contraception (defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly):

- Bilateral tubal occlusion
- Vasectomized partner
- Intra-uterine device
- Intra-uterine hormone-releasing system
- Oral combined hormonal contraception (estrogen and progestogen containing) associated with inhibition of ovulation (oral, intravaginal, transdermal)

- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Abstinence - defined as: refraining from heterosexual intercourse for the entire period of risk associated with the study treatments. Periodic abstinence is not acceptable (calendar, symptothermal, or post-ovulation methods), and neither are the withdrawal method (coitus interruptus), spermicides only, and lactational amenorrhea method. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Contraception must be effective at the first administration of magrolimab, throughout the trial and for 12 months after the last dose of rituximab, 6 months after the last dose of gemcitabine or oxaliplatin, or 4 months after the last dose of magrolimab, whichever occurs later.

Male patients with partners of childbearing potential must agree to take measures not to father children by using one of the following forms of effective contraception:

- Methods Considered Highly Effective
  (defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly)
  - Vasectomy
  - Partner with bilateral tubal occlusion
  - Abstinence
    Defined as: refraining from heterosexual intercourse for the entire period of risk associated with the study treatments. Periodic abstinence is not acceptable (calendar, symptothermal, post-ovulation methods), nor is the withdrawal method (coitus interruptus). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

- Method Not Considered Highly Effective
  (defined as methods that result in a failure rate of more than 1% per year)
  - Condom plus spermicide

Contraception must be effective at the first administration of magrolimab, throughout the trial, and for 12 months after the last dose of rituximab, 6 months after the last dose of gemcitabine or oxaliplatin, or 4 months after the last dose of magrolimab, whichever occurs later.

It should be explained to the patient that if his partner is pregnant or breastfeeding when he is enrolled on the trial, the patient should use barrier method contraception (condom plus spermicidal gel) to prevent the unborn fetus or the baby being exposed to investigational product.

Male patients must also refrain from sperm donation from the first administration of magrolimab throughout the trial and for 12 months after the last dose of rituximab, 6 months after the last dose of gemcitabine or oxaliplatin, or 4 months after the last dose of magrolimab, whichever occurs later.

4.3. Patient Screening and Enrollment Procedures

All patients who enter the screening period for the study, which starts when the patient signs the informed consent form (ICF), receive a unique patient identification number within 2 days of consent (refer to Section 4.5). This number is used to identify the patient throughout the clinical trial and must be used on all study documentation related to that patient, including if a patient is rescreened.

Patient screening laboratory assessments may be repeated beyond the initial screening assessments within the 30-day screening period. Patients who screen fail may undergo repeated screening if the patient's medical condition has changed.

All patients who provide informed consent must be registered in the electronic data capture (EDC) system, including any screen failures.

A patient is defined as enrolled in the study once all eligibility criteria have been satisfied and the patient has been registered in the interactive web response technology (IWRS) system. After signing the ICF, eligible patients are expected to receive the first dose of magrolimab (Study Day 1) within 30 days.

4.4. Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the Institutional Review Board/Research Ethics Committee (IRB/REC)-approved ICF prior to participation in any study specific procedure. Data from assessments performed as part of standard of care prior to ICF signature may be used if they are within the required screening period. The participant must receive a copy of the signed and dated consent documents. A signed copy (in paper or electronic format) of the consent documents must be retained in the medical record or research file.

4.5. Registration Process

The site will register the patient via IWRS within 2 days of consent. IWRS will assign each patient a unique patient identification number.

Prior to being assigned a dose cohort or treatment arm, patients must have signed the informed consent and satisfied all of the eligibility criteria. Once a patient has been assigned to a dose cohort, and receives the first (priming) dose, they will be considered enrolled.

5. STUDY DRUG INFORMATION

Detailed instructions for magrolimab + R-GemOx preparation and handling are provided in the Pharmacy Manual.

5.1. Study Drug: Antibody Combination (Magrolimab + Rituximab)

5.1.1. Physical Description of Study Drug

5.1.1.1. Magrolimab

The active pharmaceutical ingredient (API) is magrolimab, a humanized IgG4 mAb of the IgG4 kappa isotype containing a Ser-Pro substitution in the hinge region (position 228) of the heavy chain to reduce Fab arm exchange. It comprises a disulfide-linked glycosylated tetramer, consisting of two identical 444 amino acid

heavy gamma chains and two identical 219 amino acid kappa light chains. Magrolimab targets the human CD47 antigen. Magrolimab drug product is a sterile, clear, colorless, preservative-free liquid intended for IV infusion.

Magrolimab API is manufactured under current Good Manufacturing Practices.

Magrolimab is supplied in single-use, 10 mL vials containing 200 mg of the antibody in a formulation of 10 mM sodium acetate, 5% (w/v) sorbitol, 0.01% (w/v) polysorbate 20, at pH of 5.0.

The labeling complies with the requirements of the applicable regulatory agencies. Additional details about magrolimab are provided in the Pharmacy Manual.

5.1.1.2. Rituximab

Rituximab is a genetically engineered chimeric murine/human monoclonal IgG_1 kappa antibody directed against the CD20 antigen (Appendix A). Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration.

Rituximab is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-use vials. The product is formulated in polysorbate 80 (0.7 mg/mL), sodium chloride (9 mg/mL), sodium citrate dihydrate (7.35 mg/mL), and Water for Injection. The pH is 6.5. Diluted solutions should be stored refrigerated (2 to 8°C).

Rituximab vials (100 mg/10 mL single-use vials and 500 mg/50 mL single-use vials) are stable at 2 to 8°C (36°F to 46°F). Rituximab vials should be protected from direct sunlight.

Diluted rituximab solution should be stored at 2 to 8°C because there is no preservative. The diluted solution is stable for 24 hours at 2 to 8°C.

5.2. Study Drug: Chemotherapy Combination (Magrolimab + R-GemOx)

5.1.2. Physical Description of Study Drug

Refer to Section 5.1.1.1 and Section 5.1.1.2 for descriptions of magrolimab and rituximab, respectively.

5.1.2.1. Gemcitabine

Gemcitabine HCl (GEMZAR) is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine HCl is 2´-deoxy-2´,2´-difluorocytidine monohydrochloride (β-isomer). The empirical formula for gemcitabine HCl is C9H11F2N3O4 • HCl. It has a molecular weight of 299.66. It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents. The clinical formulation is supplied in a sterile form for IV use only. Vials of GEMZAR contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment. GEMZAR (gemcitabine for injection United States Pharmacopeia [USP]) is a white to off-white lyophilized powder available in sterile single-use vials containing 200 mg or 1 g of gemcitabine.

Additional details will be provided in a separate Pharmacy Manual.

5.1.2.2. Oxaliplatin

ELOXATIN® (oxaliplatin for injection and oxaliplatin injection) is an antineoplastic agent with the molecular formula $C_8H_{14}N_2O_4Pt$ and the chemical name of cis-[(1 R,2 R)-1,2 cyclohexanediamine-N,N'] [oxalato(2-)- O,O'] platinum. Oxaliplatin is an organoplatinum complex in which the platinum atom is complexed with 1,2-diaminocyclohexane and with an oxalate ligand as a leaving group.

The molecular weight is 397.3. Oxaliplatin is slightly soluble in water at 6 mg/mL, very slightly soluble in methanol, and practically insoluble in ethanol and acetone.

Powder for solution for infusion: ELOXATIN is supplied in vials containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free lyophilized powder for reconstitution. Lactose monohydrate is present as an inactive ingredient at 450 mg and 900 mg in the 50 mg and 100 mg dosage strengths, respectively.

Concentrate for solution for infusion: ELOXATIN is supplied in vials containing 50 mg, 100 mg, or 200 mg of oxaliplatin as a sterile, preservative-free, aqueous solution at a concentration of 5 mg/mL. Water for Injection, USP is present as an inactive ingredient.

Additional details will be provided in a separate Pharmacy Manual.

6. TREATMENT PLAN

6.1. Study Drug Administration

6.1.1. Antibody Combination (Magrolimab + Rituximab)

Planned Phase 1b dose levels for the antibody combination (magrolimab + rituximab) are outlined below in Table 6-1 and the current Phase 2 dose for the antibody combination (magrolimab + rituximab) is outlined in Table 6-2. The initial CTSC RP2DS and alternative dose regimens evaluated can be found in Appendix H. Patients enrolled under alternate schedules will have transitioned to the SOA described in Table 7-1. Details of magrolimab administration are provided in Section 6.1.1.1 and details of rituximab administration are provided in Section 6.1.1.2.

The dose of each study drug will be calculated based on actual weight at enrollment (using weight obtained either at Screening or on Day 1) and remains constant throughout the study, unless there is a > 10% change in weight from baseline.

Modifications to the study drug doses administered should be made for a > 10% change in body weight and according to local and regional prescribing standards (Appendix A). Dose modifications for changes in body weight < 10% maybe made according to local institutional guidelines.

In addition, a 90-minute rituximab infusion may be given as an alternative to standard rituximab infusion times for the Cycle 2 rituximab dose and beyond, if in accordance with local clinical guidelines.

For Phase 2, patients may be enrolled simultaneously without a dosing observation time between patients.

Magrolimab + rituximab treatment may be extended to ‘until loss of clinical benefit or unacceptable toxicity’ for patients who do not have disease progression.

Patients who develop a known adverse reaction to rituximab may continue treatment with magrolimab and will not be required to discontinue the study.

Table 6-1 Dosing: Antibody Combination (Magrolimab + Rituximab) Phase 1b

Dose Level	Drug/Dose (IV)	Dose Schedule (Day per 28-day Cycle)[a]		
		Cycle 1	Cycle 2	Cycle 3+
Phase 1b: Level 1 Priming	Magrolimab 1 mg/kg	Day 1	—	—
Maintenance	Magrolimab 10 mg/kg[a]	Day 8, 15, 22	Day 1, 8, 15, 22	Day 1, 8, 15, 22
	Rituximab 375 mg/m^2	Day 8, 15, 22	Day 1	C3-C6, Day 1
Phase 1b: Level 2 Priming	Magrolimab 1 mg/kg	Day 1	—	—
Maintenance	Magrolimab 20 mg/kg[a]	Day 8, 15, 22	Day 1, 8, 15, 22	Day 1, 8, 15, 22
	Rituximab 375 mg/m^2	Day 8, 15, 22	Day 1	C3-C6, Day 1
Phase 1b: Level 3 Priming	Magrolimab 1 mg/kg	Day 1	—	—
Maintenance	Magrolimab 30 mg/kg[a]	Day 8, 11, 15, 22	Day 1, 8, 15, 22	Day 1, 8, 15, 22
	Rituximab 375 mg/m^2	Day 8, 15, 22	Day 1	C3-C6, Day 1
Phase 1b: Level 4 Priming	Magrolimab 1 mg/kg	Day 1	—	—
Maintenance	Magrolimab 45 mg/kg[a]	Day 8, 11, 15, 22	Day 1, 8, 15, 22	Day 1, 15
	Rituximab 375 mg/m^2	Day 8, 15, 22	Day 1	C3-C6, Day 1

Abbreviations: C = cycle number; IV = intravenous; RP2DS = recommended Phase 2 dose and schedule.

a. Phase 1b patients who continue treatment in Phase 2 may follow the Phase 2 dosing schedule (i.e., at the RP2DS). In Amendment 6, rituximab dosing was added to Day 1 of every other cycle starting with Cycle 8 and beyond.

Table 6-2 Dosing: Antibody Combination (Magrolimab + Rituximab) Phase 2 Cohort 4

Drug/Dose (IV)	Dose Schedule (Day per 28-day Cycle)			
	Cycle 1	Cycle 2	Cycles 3 to 6	Cycle 7+
Magrolimab 1 mg/kg (prime)	Day 1	—	—	—
Magrolimab 30 mg/kg (maintenance)[a]	Day 8[a], 15, 22	Day 1, 8, 15, 22	Day 1,15	Day 1, 15
Rituximab 375 mg/m^2 [a]	Day 8[a], 15, 22	Day 1	Day 1 of Cycle 6, then Day 1 every other Cycle starting Cycle 8	

Abbreviations: IV = intravenous.
a. On Cycle 1 Day 8 magrolimab is to be given first, followed by rituximab. For all other times when rituximab and magrolimab are given on the same visit, rituximab should be given first. There should be at least an hour interval between the end of infusion of the first drug and the beginning of the infusion of the second drug.

6.1.1.1. Magrolimab Administration

The magrolimab dosing regimen is provided in Table 6-1 (Phase 1b) and Table 6-2 (Phase 2).

Patients will receive a priming dose of 1 mg/kg magrolimab on Day 1 of Cycle 1, and then maintenance doses:

- **Cycle 1 Day 1:** Administration of 1 mg/kg IV priming dose only; the duration of the infusion of the priming dose will be 3 hours (± 30 minutes). Repriming doses are required for patients who experience a treatment delay of longer than 2 weeks after a priming dose or longer than 4 weeks after at least 1 maintenance dose. Details are provided in Section 6.1.1.4.
- **Loading/maintenance dosing:** IV administration; the duration of the infusion of the maintenance dose will be 2 hours (± 30 minutes) except in cases outlined in the pharmacy manual.

The order of administration has been changed in Amendment 9 when both magrolimab and rituximab Phase 2 Cohort 4 and R-Gem-Ox Expansion cohort are given on Cycle 1, Day 8, magrolimab will be given first, and then, rituximab will be administered at least 1 hour after the completion of magrolimab administration. At

subsequent visits when both magrolimab and rituximab are given on the same day, rituximab will be given first followed by magrolimab at least 1 hour after the completion of rituximab infusion. If patients have unacceptable toxicity due to rituximab as determined by the treating Investigator and Sponsor, then patients may continue on study with magrolimab monotherapy. This continuation requires consultation with the Sponsor. Volume restriction may be considered for patients with cardiac, pulmonary, or other medical condition which render the patient sensitive to fluid overload. Refer to Pharmacy Manual for more information.

Patients enrolled in the Phase 1b part of the study who have been on study for at least 8 weeks may have their magrolimab dose revised to the RP2DS, at the discretion of the Investigator and the Sponsor.

All patients must have documented hemoglobin ≥ 9 g/dL within 24 hours prior to each of the first 2 doses of magrolimab infusion during initial treatment. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet 9 g/dL prior to each of the first 2 doses of magrolimab. Hemoglobin must be checked again 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment. The patient should be transfused as clinically appropriate. Investigators should consider additional hemoglobin monitoring during the first week of treatment in patients with symptoms of anemia or at increased risk for complications of anemia.

6.1.1.2. Premedication (for Magrolimab)

The optimal pretreatment regimen is defined as acetaminophen/paracetamol plus an antihistamine (i.e., oral acetaminophen 650 to 1000 mg [4 g/day maximum dose], oral or IV diphenhydramine 25 to 50 mg or comparable regimen) plus IV dexamethasone 4 to 20 mg, or comparable regimen.

- Premedication is required before administration of the first 2 doses of magrolimab.
- Premedication is also required for the repriming dose and the first maintenance dose.
- Premedication for subsequent magrolimab treatments may be continued

based on the treating physician's clinical judgement and the presence/severity of prior infusion reactions where allowed (Guidance is provided under Management of Infusion Reactions in Section 6.2.1.3).

6.1.1.3. Post-infusion Monitoring (for Magrolimab)

All patients should be monitored for 1 hour post-infusion during Cycle 1 and after any "reprime" infusion at later cycles. Post-infusion monitoring should begin after the last study drug is given. Post-infusion monitoring is not required for doses after Cycle 1 Day 22, unless the patient is "reprimed". Patients who experience any TRAEs during the observation period should be further monitored, as clinically appropriate. Patients who experience a Grade 2 infusion reaction during the post-infusion observation period that does not resolve to ≤ Grade 1 during that time should be observed until the AE resolves or stabilizes, with vital sign measurementsas medically indicated for the management of the AE.

6.1.1.4. Repriming (for Magrolimab)

The following list describes the requirements for magrolimab repriming.

- Patients who experience an interruption of >2 weeks after receiving only the priming dose (1 mg/kg) must be "reprimed" by receiving the magrolimab priming dose of 1 mg/kg IV over 3 hours (±30 minutes) and 3 subsequent weekly maintenance doses prior to starting a Q2W dosing schedule.
- Patients who experience an interruption of > 4 weeks after receiving at least 1 maintenance dose (i.e., 30 mg/kg) must be "reprimed" by receiving the magrolimab priming dose of 1 mg/kg IV over 3 hours (±30 minutes) and 3 weekly maintenance doses prior to starting the Q2W dosing schedule.
- For long-term patients (≥ 18 months therapy) who are receiving maintenance magrolimab Q4W and experience an interruption of > 6 weeks after receiving the last dose must be "reprimed" by receiving the magrolimab priming dose of 1 mg/kg over 3 hours then weekly maintenance doses prior to starting a Q4W dosing schedule.
- Rituximab must be administered as regularly scheduled (e.g., magrolimab repriming doses may be administered on the same day as rituximab is given and schedule of rituximab administration should be maintained.)

- Premedication is required for the repriming dose and the following/subsequent maintenance dose.

On the day that patients receive their repriming dose, a predose ADA sample is to be collected.

For patients who are reprimed, the following assessments are to be performed at the supplemental weekly visits (e.g., Day 8, Day 22):

- Complete blood count (CBC) with differential, platelets, reticulocytes
- Peripheral blood smear
- Serum chemistry
- Haptoglobin, D-dimer, thrombin, fibrinogen (Day 8 only)
- Prothrombin time (PT)/international normalized ratio (INR), activated partial thromboplastin time (aPTT) (Day 8 only)
- Vital signs
- Physical examination (Day 8 only)
- AEs
- Concomitant medications

The visit window for the weekly repriming visits is ± 3 days.

6.1.1.5. Rituximab Administration

Patients will receive rituximab at a dose of 375 mg/m^2 given IV starting on Day 8, followed by Days 15 and 22. Starting at Cycle 2, rituximab will be given on Day 1 of each cycle up to Cycle 6. Thereafter (i.e., Cycles 8 and beyond): administration of 375 mg/m^2 rituximab IV infusion on Day 1 of every-other-cycle (on even cycles).

In addition, a 90-minute rituximab infusion may be given as an alternative to standard rituximab infusion time for Cycle 2 dose and beyond, if in accordance with local clinical guidelines.

Rituximab will be administered until loss of clinical benefit or unacceptable toxicity. If patients have unacceptable toxicity due to rituximab as determined by the treating Investigator and Sponsor, then patients may continue on study with magrolimab monotherapy. This continuation requires consultation with the Sponsor.

6.1.2. Chemotherapy Combination (Magrolimab + R-GemOx)

Study drug administration of the combination of magrolimab + R-GemOx will be according to Table 6-3 for the safety dose-escalation and expansion phases.

Combination therapy with gemcitabine and oxaliplatin is standard of care at most centers and will not be supplied by the Sponsor. Sites that require the Sponsor to provide this combination will not be able to enroll patients in this cohort.

Table 6-3 Dosing: Chemotherapy Combination (Magrolimab + R-GemOx) Safety Dose-Escalation and Expansion Cohorts

Drug	Cycle 1 (5 weeks)	Cycle 2 (4 weeks)	Cycles 3–4 (4 weeks)	Cycles 5–6 (4 weeks)	Cycle 7+ (4 weeks)
DOSE-ESCALATION Dose Level 1: Magrolimab (IV)[a]	1 mg/kg priming: Day 1 30 mg/kg maintenance: Day 8, 11, 15, 22, 29	30 mg/kg maintenance: Day 1, 8, 15, 22	30 mg/kg maintenance: Day 1, 15	30 mg/kg maintenance: Day 1, 15	30 mg/kg maintenance: Day 1, 15
DOSE-ESCALATION Dose Level 2: Magrolimab (IV)[b]	1 mg/kg priming: Day 1 45 mg/kg maintenance: Day 8[d], 11, 15, 22, 29	45 mg/kg maintenance: Day 1, 8, 15, 22	45 mg/kg maintenance: Day 1, 15	45 mg/kg maintenance: Day 1, 15	45 mg/kg maintenance: Day 1, 15
DOSE-EXPANSION Magrolimab (IV)[c, d]	1 mg/kg priming: Day 1 30 mg/kg maintenance: Day 8, 15, 22, 29	30 mg/kg maintenance: Day 1, 8, 15, 22	30 mg/kg maintenance: Day 1, 15	30 mg/kg maintenance: Day 1, 15	30 mg/kg maintenance: Day 1, 15
Rituximab (IV)	375 mg/m^2: Day 8[d], 15, 22, 29	375 mg/m^2: Day 1	375 mg/m^2: Day 1	375 mg/m^2: Day 1 then Day 1 every other cycle starting Cycle 8	
Gemcitabine (IV)	1000 mg/m^2: Day 11, 23	1000 mg/m^2: Day 2, 15	1000 mg/m^2: Day 2, 15	-	-
Oxaliplatin (IV)	100 mg/m^2: Day 11, 23	100 mg/m^2: Day 2, 15	100 mg/m^2: Day 2, 15	-	-
G-CSF prophylaxis[e]	Administer	Administer	Administer	-	-
Allopurinol (oral)[f]	Daily	-	-	-	-

Abbreviations: CTSC = Clinical Trial Steering Committee; G-CSF = granulocyte colony stimulating factor; IV = intravenous; R-GemOx = rituximab, gemcitabine, and oxaliplatin.

a. Magrolimab maintenance dose maybe de-escalated to 20 mg/kg or 10 mg/kg with the identical dosing schedule of maintenance doses if the regimen is deemed too toxic by the CTSC.

b. The CTSC may decide to explore higher doses of magrolimab in increments up to 50% higher than the prior dose level deemed to be safe in accordance with the modified 3 + 3 design.

c. The magrolimab maintenance dose level utilized in the expansion phase will be the recommended dose selected by the CTSC from the safety dose-escalation phase.

d. On Cycle 1 Day 8 magrolimab is to be given first, followed by rituximab. For all other times when rituximab and magrolimab are given on the same visit, rituximab should be given first. There should be at least an hour interval between the end of infusion of the first drug and the beginning of the infusion of the second drug.

e. G-CSF primary prophylaxis must be administered with gemcitabine and oxaliplatin treatment. Local standard of care or equivalent will be administered in accordance to local institutional guidelines or Investigator guidance. G-CSF prophylaxis should generally occur within several days after administration of each day gemcitabine and oxaliplatin is dosed. However, the timing of G-CSF prophylaxis may be given in accordance to local institutional guidelines.

f. Allopurinol of 300 mg oral daily should be administered for the first cycle only to prevent tumor lysis syndrome associated with chemotherapy. Allopurinol may be given at 100 mg oral daily for the first cycle if significant renal impairment is present as determined by the Investigator

The dose of each study drug (magrolimab and R-GemOx) will be calculated based on actual weight at enrollment (using weight obtained either at Screening or on Day 1) and remains constant throughout the study, unless there is a 10% change in weight from baseline. Modifications to the study drug doses administered should be made for a > 10% change in body weight and according to local and regional prescribing standards (rituximab Appendix A, gemcitabine Appendix F, and oxaliplatin Appendix G). Dose modifications for changes in body weight < 10% may be made according to local institutional guidelines.

Magrolimab and rituximab treatment may extend throughout the trial for patients who do not have disease progression or who continue to have clinical benefit. Gemcitabine and oxaliplatin dosing will complete after Cycle 4; however, dosing may continue beyond Cycle 4, as needed, until a total of 8 doses have been received at the discretion of the Investigator.

Patients who develop a significant known adverse reaction to rituximab, gemcitabine, and/or oxaliplatin may discontinue that drug(s), will not be required to discontinue the study, and may continue treatment with magrolimab, rituximab, and other chemotherapy component.

Granulocyte colony stimulating factor (G-CSF) prophylaxis is required for gemcitabine and oxaliplatin dosing to mitigate myelosuppression and dose delays observed with this chemotherapy combination. G-CSF primary prophylaxis must be administered with gemcitabine and oxaliplatin treatment (Cycles 1–4, or later if dose delays). Neupogen, Neulasta, or other equivalent will be administered in accordance to local institutional guidelines or Investigator guidance. G-CSF prophylaxis should generally occur within several days after administration of each day gemcitabine and oxaliplatin is dosed. However, the timing of G-CSF prophylaxis may be given in accordance to local institutional guidelines.

6.1.3. Magrolimab Administration

The magrolimab dosing regimen for the safety dose-escalation and expansion phases of the magrolimab + R-GemOx cohort will be the same as outlined in Section 6.1.1.1.

When both magrolimab and rituximab are given on the same visit day, magrolimab will be administered at least 1 hour after the completion of the rituximab administration. When magrolimab and gemcitabine and oxaliplatin are given on the same visit day, magrolimab will be administered at least 30 minutes after the completion of gemcitabine and oxaliplatin administration.

6.1.3.1. Premedication

Premedication for magrolimab must be administered as described in Section 6.1.1.2.

6.1.3.2. Post-infusion Monitoring

Post-infusion monitoring for magrolimab should be performed as described in Section 6.1.1.3.

6.1.3.3. Repriming

Magrolimab repriming instructions are outlined in Section 6.1.1.4.

6.1.3.4. Gemcitabine Administration

In both the safety dose-escalation and expansion phases, patients will receive gemcitabine at a dose of 1000 mg/m^2 given IV. Dosing is outlined in Table 6-3. For all doses, gemcitabine will be administered over 30 minutes. Dosing administration is outlined below:

- Cycle 1: Administration of 1000 mg/m^2 IV on Days 11 and 23
- Cycles 2 through 4: Administration of 1000 mg/m^2 IV on Day 2 and 15 of each cycle

For visit days where gemcitabine and oxaliplatin are administered together (Cycle 1: Day 11 and 23) and Cycles 2 through 4: Day 2 and 15), gemcitabine should be administered first, followed by oxaliplatin infusion. On visit days where gemcitabine and oxaliplatin are administered together with magrolimab (Cycle 1 Day 11 [if applicable] and Cycles 2 through 4: Day 15), sequential gemcitabine and oxaliplatin infusions should be completed 30 minutes before the start of magrolimab administration.

6.1.3.5. Oxaliplatin Administration

In both the safety dose-escalation and expansion phases, patients will receive oxaliplatin at a dose of 100 mg/m^2 given IV. Dosing is outlined in Table 6-3. For all doses, oxaliplatin will be administered over 2 hours. Dosing administration is outlined below:

- Cycle 1: Administration of 100 mg/m^2 IV on Days 11 and 23
- Cycles 2 through 4: Administration of 100 mg/m^2 IV on Day 2 and 15 of each cycle

For visit days where gemcitabine and oxaliplatin are administered together (Cycle 1: Day 11 and 23 and Cycles 2 through 4: Day 2 and 15), gemcitabine should be administered first, followed by oxaliplatin infusion. On visit days where gemcitabine and oxaliplatin are administered together with magrolimab (Cycle 1 Day 11 [if applicable] and Cycles 2 through 4: Day 15), sequential gemcitabine and oxaliplatin infusions should be completed 30 minutes before the start of magrolimab administration.

6.1.3.6. Premedication and Required Medications

Hydration, anti-emetics, anti-microbial prophylaxis and other prophylactic supportive treatment should be administered for gemcitabine and oxaliplatin according to local institutional guidelines and drug prescribing information where appropriate.

For both the safety dose-escalation and expansion phases, allopurinol of 300 mg oral daily should be administered during the first cycle only to prevent tumor lysis

syndrome associated with chemotherapy. Allopurinol may be given at 100 mg oral daily for the first cycle if significant renal impairment is presence as determined by the Investigator.

G-CSF prophylaxis is required for gemcitabine and oxaliplatin dosing to mitigate myelosuppression and dose delays observed with this chemotherapy combination. G-CSF primary prophylaxis must be administered with gemcitabine and oxaliplatin treatment (Cycles 1–4, or later if dose delays). Neupogen, Neulasta, or other equivalent will be administered in accordance to local institutional guidelines or Investigator guidance. G-CSF prophylaxis should generally occur within several days after administration of each day gemcitabine and oxaliplatin is dosed.

However, the timing of G-CSF prophylaxis may be given in accordance to local institutional guidelines.

6.2. Dose Delays, Dose Modifications, and Safety Management Guidelines

6.2.1. Antibody Combination (Magrolimab + Rituximab)

6.2.1.1. Dose Delays

Treatment delays of more than 4 weeks (such as for an unrelated medical condition with expected recovery) require notification to the Sponsor.

6.2.1.2. Dose Modifications

Magrolimab may be withheld if treatment-emergent magrolimab-related AEs occur, which include all AEs that constitute a DLT, as defined in Section 3.1.1.1. If the severity has recovered to Grade 0 to 2 within 4 weeks and in the absence of disease progression, magrolimab may be re-introduced at a dose of 10, 20, or 30 mg/kg (i.e., the appropriate next lower dose level deemed safe by the CTSC). With 2 exceptions, patients who experience a DLT will have their treatment held for up to 4 weeks to allow sufficient time for recovery but may restart dosing at a lower dose level if they still meet study eligibility criteria. Patients who experience a DLT of either hemolytic anemia or Grade ≥ 4 non-hematological toxicity will not restart magrolimab and will be withdrawn from study drug. Data from patients who restart

dosing after the recovery period will not contribute to the MTD evaluation at the lower dose level. Patients who have dose reductions in magrolimab can re-escalate back up to the RP2DS magrolimab dose level based on Investigator's discretion with notification to the Sponsor.

An interruption is defined as a non-protocol-specified interruption from treatment, assessments, and procedures. Patients with an interruption of longer than 4 weeks or a treatment delay of longer than 4 weeks or more must be "reprimed" by receiving the priming dose of 1 mg/kg IV over 3 hours (± 30 minutes) again prior to resuming the assigned maintenance treatment dose (refer to Section 6.1.1.1).

For patients who have achieved a CR and who have been receiving study medication(s) for ≥ 18 months, the magrolimab dosing will be extended to Q4W at the discretion of the Investigator after discussion with the Medical Monitor. In this situation, the repriming requirement is extended to 6 weeks (e.g., 6 weeks exactly between doses, repriming is not required and 6 weeks + 1 day or more between doses, repriming is required).

Table 6-4 Magrolimab Dose Modifications

CTCAE Grade of Anemia	Management	Follow-Up
Grade 2 Mild-to-moderate new symptoms	Continue magrolimab and monitor signs and symptoms closely, transfuse per institutional guidelines	Monitor per institutional guidelines If worsening, follow Grade 3 or 4 guidelines
Grade 3 or 4 Severe new symptoms; new/worsening anemia; life-threatening	Contact the medical monitor for Grade 3 or 4 if a drug hold is required. Transfuse as needed and monitor until recovery	Monitor per institutional guidelines until recovery
CTCAE Grade of Thromboembolic event	**Management**	**Follow-Up**
Grade 1	Continue magrolimab and monitor signs and symptoms	Consider imaging as clinically indicated
Grade 2 Mild-to-moderate new symptoms	Continue magrolimab, monitor signs and symptoms Intervene as clinically indicated	If worsening, follow Grade 3 or 4 guidelines
Grade 3 or 4 Severe new symptoms; new/worsening; life-threatening	Contact the medical monitor for Grade 3 or 4 if a drug hold is required Monitor signs and symptoms, intervene as clinically indicated	If improving to baseline magrolimab may resume If no clinical improvement after 8 weeks or worsening, consider permanent discontinuation of magrolimab

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

Intra-patient Dose Escalation

When an RP2DS has been determined, patients enrolled in the Phase 1b part of the study who have been on study for at least 8 weeks may have their maintenance dose escalated to the dose level that has been previously determined to be safe in this study, at the discretion of the Investigator and the Sponsor.

Rituximab

Dose modifications for rituximab should be in accordance with the prescribing information (Appendix A).

6.2.1.3. Safety Management Magrolimab

For additional information regarding safety, refer to the current version of the magrolimab IB.

Thromboembolic Events

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

Severe Neutropenia

Severe neutropenia and febrile neutropenia have been reported in patients treated with magrolimab. Close monitoring of hematologic parameters (refer to Table 7-1, Table 7-2, and Table 7-5) including neutrophils is required for all patients treated with magrolimab. Prophylactic antibiotics and/or antimycotics should be considered. Administer G-CSF if clinically indicated.

Recommendations for magrolimab dose delay in case of severe neutropenia:

- For Grade 3 neutropenia (ANC <1000 to 500/μL) without fever or infection, delay of magrolimab dosing is not recommended.

- For Grade 4 neutropenia (ANC < 500/μL) without fever or infection, or Grade 3 or higher neutropenia with fever or infection, magrolimab dose delay should be considered. Upon resolution to Grade ≤ 2, resuming magrolimab at the same dose should be considered.
- For persistent severe neutropenia or febrile neutropenia (> 2 occurrences), discontinuation of magrolimab can be considered.

Serious Infections

For serious infections, hold magrolimab until the infection has resolved clinically. For serious infections that remain active for ≥ 14 days, consider discontinuation of magrolimab. Patients (with or without neutropenia) should be regularly monitored for signs and symptoms of infection. For patients with prolonged neutropenia or patients at risk, consider infection prophylaxis including antibiotics (eg, fluoroquinolone) or antifungal agents (eg, oral triazoles or parenteral echinocandin) in accordance with current guidelines.

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

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

In clinical studies, anemia is the most common treatment-related AE and is typically manifested as a decline in hemoglobin of about 0.5 g/dL to 1.5 g/dL observed in the first 1 to 2 weeks of treatment. This decrease in hemoglobin level is acceptable in patients with no other significant diseases or medical conditions. However, for patients with significant diseases or medical conditions, such as unstable angina, ischemic heart disease, or uncontrolled diabetes mellitus, treatment-related anemia could be life-threatening or fatal. Significant drops (up to 3 g/dL) have been observed in early doses.

Patients with a low baseline hemoglobin level, especially those with cardiac history

or risk factors, must be monitored closely after initial administrations of magrolimab as preexisting anemia could be exacerbated (Section 6.1.1.1). Red blood cell transfusions are permitted prior to study treatment to ensure adequate hemoglobin level per the investigator's clinical judgment. The need for RBC transfusions and anemia from other causes in patients with cancer means that care has to be taken with RBC cross-matching and packed RBC transfusions.

Prior to initiation of magrolimab, ABO/Rh type, antibody screen, DAT, and extended RBC phenotyping (including minor antigens such as CcDEe, Cw, MNSs, Kk, FyaFyb, and JkaJkb) will be performed for each patient (Section 7.3.4). Red blood cell genotyping instead of extended RBC phenotyping is acceptable for any patient. Red blood cell genotyping (instead of an extended RBC phenotyping) must be performed if a patient received any RBC or whole blood transfusion within the previous 3 months (unless laboratory has availability for special techniques for performing phenotyping for patients with recent transfusion). Results must be available before the first dose of magrolimab.

For patients after exposure to magrolimab:
For all elective RBC and platelet transfusions, use leukocyte-reduced and gamma-irradiated units per institutional guidelines. For RBCs, phenotype/genotype matched units are preferred. However, CMV-seronegative units for CMV-seronegative patients will not be required for this study.

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

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

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

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

Blood Components for Transfusion

For all elective red cell transfusions, leukocyte-reduced units matched for the phenotype of the patients (as described above) will be used. Where exact matching for all the specified blood groups proves impractical (e.g., for MNS blood group), local sites will decide on the best matched donor units to be used. Cytomegalovirus (CMV) matching (i.e., CMV seronegative units for CMV-seronegative patients) will not be required for this study because it will limit the inventory for antigen matching.

If the cross match is incompatible, the RBC units that are Coombs cross-match incompatible will be selected (e.g., phenotype-matched or least incompatible) for issue at the discretion of the local site's Transfusion Service Medical Director or equivalent person, where available.

For emergency transfusions, the transfusion laboratory may consider using emergency Group O Rhesus negative units if phenotyped units are not available.

Blood plasma therapy will be blood type specific. Platelets will be blood type compatible whenever possible, and if not, will have been tested and found not to have high titer anti-A or anti-B.

Management of Infusion Reactions

Infusion-related reactions are defined by the NCI CTCAE (under the category "General disorders and administration site conditions") as "a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances" (Appendix B). For the purposes of this study, the time frame for infusion reaction assessment is the 24-hour period beginning from the start of the infusion. Recommendations for the management of IRRs are provided below.

- For Grade 1 IRRs, described as mild transient reaction, infusion interruption is not indicated and intervention is not indicated:

- Remain at bedside and monitor patient until recovery from symptoms.
- Patients who experience IRRs with the first 2 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion.

- For Grade 2 IRRs, infusion interruption is indicated, but patient responds promptly to symptomatic treatment (e.g., antihistamines, acetaminophen,narcotics, corticosteroids, IV fluids); and prophylactic medications are indicated for ≤ 24 hours:
  - Stop the magrolimab infusion, begin an IV infusion of normal saline, and consider treating the patient with diphenhydramine 25 to 50 mg IV (or equivalent) and/or 500 to 1000 mg oral acetaminophen (4 g/day maximum dose).
  - Remain at bedside and monitor patient until resolution of symptoms.
  - Corticosteroid therapy may also be given at the discretion of the Investigator.
  - If the infusion is interrupted, wait until symptoms resolve, then restart the infusion at 50% of the original infusion rate.
  - If no further complications occur after 1 hour (± 10 minutes), the rate may be increased to 100% of the original infusion rate. Monitor the patient closely.
  - If symptoms recur, stop infusion and disconnect patient from the infusion apparatus. No further magrolimab will be administered at that visit.
  - Patients who experience IRRs with the first 2 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion.
  - The amount of magrolimab infused must be recorded on the electronic case report form (eCRF).
  - Patients who experience a Grade 2 infusion reaction during the post-infusion observation period that does not resolve during that time should be observed until the AE resolves or stabilizes to ≤ Grade 1, with vital sign measurements as medically indicated for the management of the AE.

- For Grade 3 or Grade 4 IRRs, where:
  Grade 3 is described as prolonged IRRs (e.g., not rapidly responsive to

symptomatic medication and/or brief interruption of infusion), or recurrence of symptoms following initial improvement, or where hospitalization is indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates). Grade 4 is described as having life-threatening consequences and where urgent intervention is indicated.

- Immediately discontinue infusion of magrolimab.
- Begin an IV infusion of normal saline, and consider treating the patient as follows:
    - Administer bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 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 plus ranitidine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.
    - The patient should be monitored until the Investigator is comfortable that the symptoms will not recur.
    - Patients who experience Grade 3 infusion reactions must be given premedication prior to all subsequent doses. In this setting, premedication with oral acetaminophen (650 to 1000 mg, 4 g/day maximum dose), oral or IV diphenhydramine (25 to 50 mg [or equivalent] with or without ranitidine), and IV dexamethasone 4 to 20 mg, or a comparable regimen, is recommended for the subsequent 2 doses. Continued premedication with corticosteroids beyond these 2 doses may be administered at the discretion of the treating physician.
    - Patients who receive premedication and still experience a recurrent Grade 3 or patients who experience a Grade 4 infusion reaction at any time will be permanently discontinued from study treatment.
    - For anaphylaxis, Investigators should follow their institutional guidelines for treatment.
    - All patients who experience Grade 3 or greater IRRs will be observed until the AE resolves or stabilizes, with vital sign

measurements and additional evaluations as medically indicated for the management of the AE(s).

Post-infusion Observation Period

All patients should be monitored for 1 hour post-infusion during Cycle 1 and after any “reprime” infusion at later cycles.

Patients who experience a Grade 2 infusion reaction during the post-infusion observation period that does not resolve to ≤ Grade 1 during that time should be observed until the AE resolves or stabilizes, with vital sign measurements as medically indicated for the management of the AE.

Tumor Lysis Syndrome

In the case of evidence for tumor lysis syndrome associated with magrolimab, patients will be admitted to the hospital as clinically indicated. Standard management will include vigorous IV hydration; correction of acidosis, if present; hypouricemic agents; and close monitoring of serum uric acid, phosphorus, and electrolytes. Study treatment should be held until the patient’s condition resolves or stabilizes.

Rituximab

Administration, Hypersensitivity, and Infusion Reactions

Available at the bedside prior to rituximab administration should be epinephrine for subcutaneous injection, diphenhydramine hydrochloride for IV injection, and resuscitation equipment for the emergency management of anaphylactoid reactions. Premedication with an antihistamine and acetaminophen/paracetamol is required prior to rituximab dosing, in accordance with local best practices. Rituximab should be administered IV through a dedicated line at an initial rate of 50 mg/hour.

If hypersensitivity or infusion-related events do not occur, infusion rate may be escalated in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. If hypersensitivity or infusion-related events develop, the infusion should be temporarily slowed or interrupted. The patient should be treated according to the appropriate standard of care. The infusion can be

continued at one-half the previous rate when symptoms resolve. Subsequent rituximab infusions can be administered at an initial rate of 100 mg/hour and increased at 30-minute intervals by 100-mg/hour increments to a maximum of 400 mg/hour. If, in accordance with local clinical guidelines, a 90-minute rituximab infusion is given and the patient experiences an infusion reaction, refer to local prescribing information for infusion adjustments (Appendix A).

During the rituximab infusion, the patient should be monitored until the infusion is discontinued according to standard practice guidelines for rituximab. Following the antibody infusion, the IV line should be maintained for medications as needed. If there are no complications after 1 hour of observation, the IV line may be discontinued. Additional details about rituximab infusion are provided in Appendix A.

Presence of Circulating Lymphoma Cells

In patients with evidence of circulating lymphoma cells in the peripheral blood, it is recommended that the initial infusion rate be reduced to 25 mg/hour as these patients may have increased propensity to infusion reactions and tumor lysis syndrome.

Cardiovascular

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of rituximab. Patients with preexisting cardiac conditions, including arrhythmias and angina, and who have had recurrences of these events during rituximab therapy, should be monitored throughout the infusion and immediate post-infusion period.

Tumor Lysis Syndrome

Rituximab rapidly decreases the number of benign and malignant CD20 positive cells. Tumor lysis syndrome has been reported to occur within 12 to 24 hours after the first rituximab infusion in patients with high numbers of circulating malignant lymphocytes. Patients with high tumor burden (bulky lesions) may also be at risk. Patients at risk of developing tumor lysis syndrome should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should

be provided for patients who develop tumor lysis syndrome. Following treatment for and resolution of tumor lysis syndrome, subsequent rituximab therapy was administered in conjunction with prophylactic therapy for this syndrome in a limited number of cases.

6.2.2. Chemotherapy Combination (Magrolimab + R-GemOx)

6.2.2.1. Dose Delays

This section provides information related to dose delays for the chemotherapy combination (magrolimab + R-GemOx) cohort only. Dose delay information for the antibody combination (magrolimab + rituximab) cohort is provided in Section 6.2.1.1. Treatment delays of more than 4 weeks or 5 weeks for CR patients who have received study drugs ≥18 months and are on a 4 weekly cycle of magrolimab (such as for an unrelated medical condition with expected recovery) require notification to the Sponsor.

Magrolimab and/or Rituximab Dose Delays

No specific dose delays for magrolimab and rituximab are required. Treatment interruption for magrolimab and rituximab is allowed after the start of Cycle 3 at the discretion of the Investigator and with Sponsor approval. An interruption is defined as a non-protocol-specified interruption from treatment, assessments, and procedures. Patients with an interruption of longer than 4 weeks (2 weeks is maximum allowed for an elective drug treatment interruption), or a treatment delay of longer than 4 weeks or more, must be “reprimed” by receiving the priming dose of 1 mg/kg IV over 3 hours (± 30 minutes) again before resuming the assigned maintenance treatment dose (refer to Section 6.1.1.4). For patients who are in CR and have been on study treatment for ≥ 18 months and are receiving magrolimab Q4W, the repriming window has been extended to 6 weeks (i.e., repriming is necessary if the dose interruption is longer than 6 weeks). For patients on a priming/maintenance/loading dose cohort who have an interruption, the maintenance dose will be resumed after repriming.

Gemcitabine and/or Oxaliplatin Dose Delays

Patients should receive a total of 8 gemcitabine and oxaliplatin doses; however, fewer than 8 doses may be administered at the discretion of the Investigator. Patients should be returned to their Q2W gemcitabine and oxaliplatin schedule as soon as possible after missed, held, or delayed doses at the discretion of the Investigator. Gemcitabine and oxaliplatin dosing may continue beyond Cycle 4, as needed, until a total of 8 doses have been received at the discretion of the Investigator.

If gemcitabine and oxaliplatin dosing is delayed and doses are given at supplemental visits (e.g., Day 8 or Day 22), the following assessments (laboratory tests or other) are required:

- CBC with differential, platelets, reticulocytes
- Serum chemistry
- Vital signs
- Physical examination
- AEs
- Concomitant medications

Gemcitabine and oxaliplatin dosing should be delayed for either or both of the following hematologic toxicities:

- Platelets $<50 \times 10^9$/mL
- ANC $<1 \times 10^9$/mL

Patients can resume gemcitabine and oxaliplatin dosing when the platelets are $> 50 \times 10^9$/mL and the ANC is $> 1 \times 10^9$/mL. Magrolimab and rituximab doses do not need to be delayed for recovery of platelets and ANC as above. This dose delay guidance applies for gemcitabine and oxaliplatin only. If gemcitabine and oxaliplatin are delayed, magrolimab and rituximab should generally continue to be administered on schedule.

Additional growth factor support (G-CSF), in addition to the mandated G-CSF prophylaxis, may be given in any cycle at the discretion of the Investigator. In general, if gemcitabine and oxaliplatin dosing is delayed, magrolimab and rituximab will continue to be administered on schedule. Possible exceptions

should be discussed with the Sponsor. Dose reductions in gemcitabine and/or oxaliplatin doses are to be considered according to the guidelines provided in Table 6-5.

Table 6-5 Dose Reductions for Gemcitabine and Oxaliplatin for Hematologic Toxicities

Drug[a]	Guidance	Dose Reduction
Gemcitabine (IV) 1000 mg/m^2	Dose delay of >2 weeks occurs for the first time	No dose reduction is required, consider additional G-CSF support in addition to prophylaxis
	Dose delay of >2 weeks occurs for the second time	20% total dose reduction to 800 mg/m^2
	After 20% dose reduction, if subsequent dose is delayed for >2 weeks	50% total dose reduction to 500 mg/m^2
	After 50% dose reduction, if subsequent dose is delayed for >2 weeks	Discontinue gemcitabine
Oxaliplatin (IV) 100 mg/m^2	Dose delay of >2 weeks occurs for the first time	No dose reduction is required, consider additional G-CSF support in addition to prophylaxis
	Dose delay of >2 weeks occurs for the second time	20% total dose reduction to 80 mg/m^2
	After 20% dose reduction, if subsequent dose is delayed for >2 weeks	50% total dose reduction to 50 mg/mg^2
	After 50% dose reduction, if subsequent dose is delayed for >2 weeks	Discontinue oxaliplatin

Abbreviations: G-CSF = granulocyte colony stimulating factor; IV = intravenous.

a. For dose delays as above for hematologic toxicities, both gemcitabine and oxaliplatin should in general be dose reduced. Exceptions may occur where dose reduction for hematologic toxicity would occur for either gemcitabine or oxaliplatin and should be discussed with the Sponsor. For other (non-hematologic) toxicities specific to gemcitabine and/or oxaliplatin, dose reductions can follow the above when deemed appropriate by the treating physician. Dose reductions different from Table 6-5 should be discussed and approved by the Sponsor.

6.2.2.2. Dose Modifications

Dose modifications for rituximab, gemcitabine, or oxaliplatin should be in accordance with the respective prescribing information. However, specific dose reductions for hematologic toxicities due to gemcitabine and oxaliplatin should be followed as according to Table 6-5.

For patients with renal impairment, no dose reductions are required for creatinine clearance > 30 mL/min. For creatinine clearance ≤ 30 mL/min, dose reductions for gemcitabine and/or oxaliplatin may be considered by the treating Investigator with approval from the Sponsor.

Dose modifications or discontinuations of gemcitabine and/or oxaliplatin for other toxicities related to study drug may be instituted based on local institutional guidelines and the discretion of the Investigator.

For patients who have achieved a CR and who have been receiving study medication(s) for 18 months or longer, the magrolimab dosing will be extended to Q4W at the discretion of the Investigator after discussion with the Medical Monitor. In this situation, the repriming requirement is extended to 6 weeks (e.g., 6 weeks exactly between doses, repriming is not required and 6 weeks + 1 day or more between doses, repriming is required).

6.2.2.3. Safety Management

If unacceptable toxicities occur, gemcitabine, oxaliplatin, and/or rituximab may be discontinued while continuing magrolimab treatment, according to Investigator's discretion with approval from the Sponsor. If unacceptable toxicities occur with gemcitabine and/or oxaliplatin, treatment with magrolimab and rituximab may be continued according to Investigator discretion with approval from the Sponsor.

Magrolimab

Safety management guidelines for magrolimab are provided in Section 6.2.1.3.

Rituximab

Safety management guidelines for rituximab are provided in Section 6.2.1.3.

Gemcitabine

Treatment precautions for gemcitabine should be taken in accordance with the gemcitabine US prescribing information (Appendix F) and local institutional guidelines. Several specific precautions are outlined below.

If capillary leak syndrome, posterior reversible encephalopathy syndrome, or hemolytic-uremic syndrome is observed, discontinue treatment with gemcitabine. Consider discontinuing gemcitabine treatment for severe renal impairment or severe hepatic toxicity.

Exacerbation of Radiation Toxicity

Gemcitabine may cause severe and life-threatening toxicity when administered concurrently or within 7 days of radiation therapy. Local radiation therapy is not to be administered in the magrolimab + R-GemOx cohort within 7 days of gemcitabine administration.

Tumor Lysis Syndrome

Tumor lysis syndrome may occur with cytotoxic chemotherapy agents. Allopurinol is administered for the first cycle in the magrolimab + R-GemOx cohort as prophylaxis. Standard management will include vigorous IV hydration; correction of acidosis, if present; hypouricemic agents; and close monitoring of serum uric acid, phosphorus, and electrolytes. Patients will be admitted to the hospital as clinically indicated. Study treatment should be held until the patient's condition resolves or stabilizes.

Oxaliplatin

Treatment precautions for oxaliplatin should be taken in accordance with the oxaliplatin US prescribing information (Appendix G) local institutional guidelines. Several specific precautions are outlined below.

Hypersensitivity

If significant hypersensitivity to oxaliplatin is observed, treatment should be administered with antihistamine and corticosteroid. At the physician's discretion, the patient may be re-challenged with oxaliplatin on the next dose with the following premedication prescribed or per local institutional guidelines: Dexamethasone 4 mg oral every 6 hours x 3 doses starting 24 hours pretreatment, plus 8 mg IV 30 minutes predose.

Peripheral Neuropathy

Oxaliplatin dose should be reduced by 20% for Grade 2 or higher neuropathies that are persistent (>14 days). Oxaliplatin should be discontinued if there is persistent symptomatic paresthesia or other severe neurotoxicity despite a 20% oxaliplatin dose attenuation.

Acute Laryngopharyngeal Dysesthesia

Some patients experience laryngopharyngeal dysesthesia (unpleasant sensations in the throat) with oxaliplatin. Onset is typically during or within hours of infusion and resolves within minutes to a few days. Symptoms are exacerbated by cold, so patients should be well advised on precautions. If this finding occurs, subsequent infusions of oxaliplatin should be given over an extended time of 6 hours. These findings do not require treatment or dose reduction. Treatment may be given at clinician's discretion and can include anxiolytics and/or observation.

Tumor Lysis Syndrome

Tumor lysis syndrome may occur with cytotoxic chemotherapy agents. Allopurinol is administered for the first cycle in the magrolimab + R-GemOx cohort as prophylaxis. Standard management will include vigorous IV hydration; correction of acidosis, if present; hypouricemic agents; and close monitoring of serum uric acid, phosphorus, and electrolytes. Patients will be admitted to the hospital as clinically indicated. Study treatment should be held until the patient's condition resolves or stabilizes.

6.3. Prohibited Medication

6.3.1. Magrolimab

Anti-cancer therapies (including chemotherapy, hormonal therapy, and investigational agents) are prohibited within 4 weeks or within at least 4 half-lives (up to a maximum of 4 weeks), whichever is longer, before magrolimab administration and during the study. However, low dose steroids (oral prednisone or equivalent ≤ 20 mg per day), localized non-CNS radiotherapy, previous hormonal therapy with LHRH agonists for prostate cancer, and treatment with bisphosphonates and RANKL inhibitors are not criteria for exclusion of patients from the study and are permitted during the study. Steroid doses higher than 20 mg prednisone equivalent per day may be administered for management of clinical conditions for a temporary period if deemed clinically necessary by the Investigator with approval from the Sponsor.

6.3.2. Rituximab

Because the safety of immunization with live viral vaccines following rituximab therapy has not been studied, vaccination with live virus vaccines is not recommended while the patient is being treated with rituximab or while peripherally B cell depleted (Appendix A).

6.3.3. Gemcitabine and Oxaliplatin

There are no prohibited medications specific for gemcitabine and oxaliplatin in addition to what is already defined in this section.

Gemcitabine and warfarin precaution: Gemcitabine may increase anticoagulant effect/increased bleeding risk with gemcitabine due to decreased hepatic metabolism of warfarin. Monitor INR regularly and adjust warfarin dosage as appropriate.

For gemcitabine, radiation therapy that is allowed on study should not be administered within 7 days of gemcitabine dosing. Clinical studies have shown that concurrent administration of radiation therapy with gemcitabine can lead to increased toxicities (Appendix F). If radiation therapy within 7 days of gemcitabine dosing is needed for clinical care based on the overall risk:benefit profile, approval must be given by the Sponsor.

Oxaliplatin and nephrotoxic drugs precaution: Nephrotoxic drugs (e.g., aminoglycosides, amphotericin, furosemide, non-steroidal anti-inflammatory drugs, and others) may lead to additive nephrotoxicity with oxaliplatin. Avoid combination if possible or monitor renal function closely.

6.4. Duration of Treatment

Patients may continue to receive combination magrolimab and rituximab treatment for as long as they tolerate it, for the duration of the trial. Gemcitabine and oxaliplatin dosing are intended to complete after Cycle 4; however, dosing may continue beyond Cycle 4, as needed, until a total of 8 doses have been received at the discretion of the Investigator. Patients who do not tolerate one of the study treatment drugs may continue the other study treatment drug for the duration of the trial, if the Sponsor and Principal Investigator agree.

6.5. Patient Completion of the Study

Patients who have not demonstrated disease progression may continue to receive magrolimab and/or rituximab treatment. All patients will be followed through completion of all study treatment. Patients with ongoing serious adverse events (SAEs) and drug-related AEs will be followed for safety as outlined in Section 9.2.1.

Patients are considered to have completed study participation when they finish the Safety Follow-up Visit, as outlined in Section 7.4.

7. STUDY EVALUATIONS

7.1. Schedules of Assessments

7.1.1. Antibody Combination (Magrolimab + Rituximab): Schedules of Assessments

The SOAs for both Phase 1b and Phase 2 of the antibody combination (magrolimab + rituximab) are presented in the following tables:

Table 7-1. Antibody Combination (Magrolimab + Rituximab): RP2DS Phase 2 Schedule of Assessments (Including Phase 2 Cohort 4)

Table 7-2. Post-treatment Assessments: All Cohorts – Antibody Combination (Magrolimab + Rituximab) Phase 1b and Phase 2 and Chemotherapy Combination (Magrolimab + R-GemOx) Phase 1b

Table 7-3. Pharmacokinetic Assessments: Chemotherapy Combination (Magrolimab + R-GemOx) Phase 1b and Antibody Combination (Magrolimab + Rituximab) Phase 2

Table 7-4. Correlative Studies: All Cohorts – Antibody Combination (Magrolimab + Rituximab) Phase 1b and Phase 2 and Chemotherapy Combination (Magrolimab + R-GemOx) Phase 1b

Unless otherwise noted, procedures are to be completed prior to any study drug infusion.

7.1.2. Chemotherapy Combination (Magrolimab + R-GemOx): Schedules of Assessments

The SOAs for the chemotherapy combination (magrolimab + R-GemOx) are presented in the following tables:

Table 7-2. Post-treatment Assessments: All Cohorts – Antibody Combination (Magrolimab + Rituximab) Phase 1b and Phase 2 and Chemotherapy Combination (Magrolimab + R-GemOx) Phase 1b

Table 7-3. Pharmacokinetic Assessments: Chemotherapy Combination (Magrolimab + R-GemOx) Phase 1b and Antibody Combination (Magrolimab + Rituximab) Phase 2

Table 7-4. Correlative Studies: All Cohorts – Antibody Combination (Magrolimab + Rituximab) Phase 1b and Phase 2 and Chemotherapy Combination (Magrolimab + R-GemOx) Phase 1b

Table 7-5. Chemotherapy Combination (Magrolimab + R-GemOx): Phase 1b Schedule of Assessments, Safety Dose-Escalation and Expansion Cohorts

7.1.3. Historical Arms: Schedule of Assessments

A listing of SOA from Phase 1b studies that are no longer enrolling and with patients in long-term follow up can be found in Appendix H.

Table 7-1 Antibody Combination (Magrolimab + Rituximab): RP2DS Phase 2 Schedule of Assessments (Including Phase 2 Cohort 4)

Examination																
Cycle (28-day Cycles)		1					2				3		4		5+	
Cycle Day	SC	1	2	8	15	22	1	8	15	22	1	15	1	15	1	15[a]
Visit Window (Days)	-30	None	±1	±2			±1	± 2								
Assessments																
Informed consent[b]	X															
Demographics	X															
Medical and cancer history	X															
Inclusion/exclusion criteria	X															
Enrollment cohort assignment[b]	X															
Pregnancy test[c]	X	X[d]					X				X		X		X	
CBC with differential, platelets, reticulocytes[c]	X	X[s]	X	X[t]	X	X	X	X	X	X	X	X	X	X	X	X
Pre-infusion peripheral blood smear[e]		X[c]	X	X												
Serum or plasma chemistry[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum uric acid, phosphorous[c]	X	X	X	X	X											
Haptoglobin, D-dimer, thrombin time and plasma fibrinogen[c]	X	X	X	X	X											
PT/INR, aPTT[c]	X			X												
Type and screen (ABO/Rh), DAT, phenotyping/ genotyping[u]	X															
Lymphocyte subset analysis[f]		X					X				X		X		X	
Peripheral blood CD20+ enumeration[g]		X					X				X		X		X	
Urinalysis[c]	X				X											
Correlative studies[h]		X			X		X				X					

Examination																
Cycle (28-day Cycles)		1					2				3		4		5+	
Cycle Day	SC	1	2	8	15	22	1	8	15	22	1	15	1	15	1	15[a]
Visit Window (Days)	-30	None	±1	±2			±1	± 2								
Assessments																
Pharmacokinetics[i]		X		X	X		X		X		X		X		X[j]	
Antidrug antibodies		X					X				X				X[j]	
ECOG performance status[k]	X	X		X	X	X	X				X		X		X	
Vital signs[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[m]	X	X[c]		X	X	X	X		X		X	X	X	X	X	X
ECG[n]	X															
Tumor/lymph node biopsy[o]	X							X								
Diagnostic imaging and response assessment	X										X[p]				X[p]	
Bone marrow biopsy[q]	X										X[r]					
Adverse events	←	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►
Concomitant medications	←	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►
Study Drug Administration																
Rituximab				X[s]	X	X	X				X		X		C5 and C6, then Q2C	
Magrolimab		X		X[s]	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ABO = any of the four blood groups A, B, AB, and O; aPTT = activated partial thromboplastin time; C = cycle number; CBC = complete blood count; CR = complete response; DAT = direct antiglobulin test; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology group; PT/INR = prothrombin time/international normalized ratio; PE = physical exam; PI = Principal Investigator; PK = pharmacokinetics; PR = partial response; Q2C = every 2 cycles; RBC = red blood cell; Rh = Rhesus factor; RP2DS = recommended Phase 2 dose and schedule; SC = screening.

NOTE: Patients who will be transitioned from Phase 1b to Phase 2 dosing may have rituximab extended dosing that occurs on odd cycles rather than even (i.e., dosing on odd cycles will not be considered a protocol deviation); refer to Section 6.2.1.2.

a. No assessment should be performed at C18+ D15 when magrolimab is dosed at D1 only.

b. First dose of magrolimab must be given within 30 days of signing informed consent.

c. Pre-infusion assessments may be performed up to 72 hours before study drug administration during the initial dose, however with subsequent doses, pre-infusion assessments may be performed up to 24 hours before study drug administration.

d. May use screening pregnancy test performed within 72 hours of first dose.
e. Peripheral blood smear slides will be read locally for results and retained. Details are provided in Section 7.3.7.
f. Lymphocyte subset analysis every cycle for Cycle 1 to Cycle 6, prior to administration of study drug; following Cycle 6, analyses are at the discretion of the PI.
g. For sites that have the capability of local CD20+ testing, CD20+ B lymphocyte cell enumeration in the peripheral blood every cycle for Cycle 1 to Cycle 6, prior to administration of study drug; following Cycle 6, analyses are at the discretion of the PI. Following Cycle 18, analyses are not required. CD20+ B-cell enumeration at safety follow-up visit. Both absolute and % of lymphocytes are preferred.
h. Time point details for correlative studies are provided in Table 7-4.
i. Time point details for PK time points are provided in Table 7-3.
j. Starting with Cycle 5, samples to be collected Cycle 5 Day 1, Cycle 9 Day 1, Cycle 13 Day 1, then discontinue until safety follow-up visit. For patients who are in CR and have been on study treatment for ≥ 18 months and are receiving magrolimab Q4W, an additional ADA sample is to be collected at the third cycle Day 1 since 4-week dosing was started.
k. ECOG performance status is not required for patients who have completed more than 18 cycles.
l Prior to infusion of study drug. Details are provided in Section 7.3.2.
m. Full PE at screening, symptom-directed PE thereafter.
n. Single ECG at screening.
o. Two tumor/lymph node biopsies are mandatory during the study, one within the screening period and a second on-treatment (Cycle 2 Day 8, -1 to +3 weeks) unless determined to not be feasible by the Investigator. For patients who achieve a PR or CR, CCI [redacted] For core biopsies, in addition to a specimen that is sent to the central laboratory, local lymphoma immunophenotyping panel is requested (see Appendix I). For large excisional biopsy, a portion of the specimen is to be sent for local lymphoma immunophenotyping panel, and the remainder of the tissue is to be processed and sent to central laboratory per tissue collection guidance.
p. Response assessments at Cycle 3 Day 1 (± 7 days) then Q2C (± 7 days). Assessments may be adjusted by ± 4 weeks to coordinate with treatment cycle timing. Note that patients may be on odd or even cycles based on whether rituximab is being added back on even or odd cycles (post Cycle 6) for some patients. For patients who continue on study medications for ≥18 months, response assessment may be extended to every 3 to 4 cycles at the discretion of the Investigator. Details are provided in Section 7.3.5.
q. Bone marrow biopsy will be performed for response assessment in those patients with known bone marrow disease involvement and also performed to confirm CR at any response assessment, where clinically appropriate, and at disease progression.
r. To be performed with diagnostic imaging (± 7 days from Cycle 3, Day 1).
s. On Cycle 1 Day 8 only, magrolimab should be given prior to rituximab. All other times when magrolimab and rituximab are given on the same visit, rituximab should be given before magrolimab. There should be at least an hour interval between the end of infusion of the first drug and the beginning of infusion of the second drug.
t Within 24 hours prior to each of the first 2 doses of magrolimab infusion during initial treatment (Days 1 and 8), all patients must have a documented hemoglobin ≥ 9.0 g/dL (Section 6.1.1.1). Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet 9.0 g/dL prior to each of the first 2 doses of magrolimab. An additional hemoglobin must be checked 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment (Days 1 and 8). The patient should be transfused as clinically appropriate. Investigators should consider additional hemoglobin monitoring during the first week of treatment in patients with symptoms of anemia or at increased risk for complications of anemia.
u. ABO/Rh type, antibody screen, DAT, and extended RBC phenotyping (including minor antigens such as CcDEe, Cw, MNSs, Kk, FyaFyb, and JkaJkb) will be performed for each patient. RBC genotyping instead of extended RBC phenotyping is acceptable for any patient. A RBC genotyping (instead of an extended RBC phenotyping) must be performed if a patient received any RBC or whole blood transfusion within the previous 3 months (unless laboratory has availability for special techniques for performing phenotyping for patients with recent transfusion).

Table 7-2 Post-treatment Assessments: All Cohorts – Antibody Combination (Magrolimab + Rituximab) Phase 1b and Phase 2 and Chemotherapy Combination (Magrolimab + R-GemOx) Phase 1b

Examination	Post-treatment Assessments: All Cohorts – Antibody Combination (Magrolimab + Rituximab) Phase 1b and Phase 2 and Chemotherapy Combination (Magrolimab + R-GemOx) Phase 1b
Cycle (28-day Cycles)	**Safety Follow-up[a]**
	30 Days After Last Dose of theLast Study Drug[a]
Visit Window	**± 7 Days**
Assessments	
Serum or urine pregnancy test	X
CBC with differential, platelets, retics	X
Serum or plasma chemistry	X
Pharmacokinetics	X
Antidrug antibodies	X
ECOG performance status	X
Vital signs	X
Physical examination (symptom-directed)	X
Diagnostic imaging	X[b]
Response assessment	X[b]
Adverse events	X
Concomitant medications	X

Abbreviations: CBC = complete blood count; ECOG = Eastern Cooperative Oncology Group; R-GemOx = rituximab, gemcitabine, and oxaliplatin.

a. Safety Follow-up should occur at 30 ± 7 days; however, the follow-up may occur at an earlier time point if the patient is starting a new therapy.

b. Required only if not completed within the last 4 weeks.

Table 7-3 Pharmacokinetic Assessments: Chemotherapy Combination (Magrolimab + R-GemOx) Phase 1b and Antibody Combination (Magrolimab + Rituximab) Phase 2

	Cycle 1			Cycle 2		Cycle 3 to Cycle 6	Cycles 9 and 13	Cycle X, X+1, and X+2 [c]
Day	**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**
Before rituximab infusion (within 12 hours)		X	X	X		X[b]		
Before magrolimab infusion (within 12 hours)	X	X [a]	X [a]	X [a]	X	X [a,b]	X [b]	X

Abbreviations: PK = pharmacokinetic(s); R-GemOx = rituximab, gemcitabine, and oxaliplatin.

a. Sample to be collected before rituximab infusion when applicable. On days when both rituximab and magrolimab are administered, PK samples for rituximab and magrolimab can be combined in a single blood draw taken prior to administration of either drug.

b. Starting with Cycle 5, samples to be collected Cycle 5 Day 1, Cycle 9 Day 1, Cycle 13 Day 1, then discontinue until safety follow-up.

c. For patients who are in CR and have been on study treatment for ≥ 18 months and are receiving magrolimab Q4W, additional PK samples are to be collected. Since some patients are ongoing longer than 18 months, the table refers to the cycle that 4-week dosing starts as referred to as Cycle X. The PK samples should only be collected for 3 cycles.

Table 7-4 Correlative Studies: All Cohorts – Antibody Combination (Magrolimab + Rituximab) Phase 1b and Phase 2 and Chemotherapy Combination (Magrolimab + R-GemOx) Phase 1b

Time Points	Cycle 1		Cycle 2	Cycle 3	Cycle X, X+1, and X+2 [c]
Day	**1**	**15**	**1**	**1**	**1**
Phase 1b					
Pre-study drug infusion[a]	X	X	X	X [b]	X
Phase 2					
Pre-study drug infusion[a]	X	X	X	X[b]	X

Abbreviations: R-GemOx = rituximab, gemcitabine, and oxaliplatin; RO = receptor occupancy.

a. Cycle 1 Day 1 pre-infusion laboratory tests may be collected up to 72 hours before study drug treatment.

b. To be performed with diagnostic imaging (± 7 days from Cycle 3, Day 1).

c. For patients who are in CR and have been on study treatment for ≥ 18 months and are receiving magrolimab Q4W, additional RO samples are to be collected. Since some patients are ongoing longer than 18 months, the table refers to the cycle that 4-week dosing starts as referred to as Cycle X. The RO samples should only be collected for 3 cycles.

Table 7-5 Chemotherapy Combination (Magrolimab + R-GemOx): Phase 1b Schedule of Assessments, Safety Dose-Escalation and Expansion Cohorts

Examination	Chemotherapy Combination (Magrolimab + R-GemOx): Phase 1b Schedule of Assessments, Safety Dose-Escalation and Expansion Cohorts																									
Cycle (28-day cycles) except for Cycle 1 (35 days)		1								2					3			4			5			6+	
Cycle day	SC	1	2	8	11	15	22	23	29	1	2	8	15	22	1	2	15	1	2	15	1	15	1	15
Visit window (days)	-30	None	±1	±2						±1	±2													
Assessments																								
Informed consent[a]	X																							
Demographics	X																							
Medical and cancer history	X																							
Inclusion/exclusion criteria	X																							
Enrollment cohort assignment[a]	X																							
Pregnancy test[b]	X	X[c]								X					X			X			X		X	
CBC with differential, platelets, reticulocytes[b, u]	X	X[u]	X	X[u]		X	X		X	X			X		X		X	X		X	X	X	X	X
Peripheral blood smear[d]		X[b]	X	X																				
Serum or plasma chemistry[b]	X	X	X	X		X	X		X	X			X		X		X	X		X	X	X	X	X

Examination	Chemotherapy Combination (Magrolimab + R-GemOx): Phase 1b Schedule of Assessments, Safety Dose-Escalation and Expansion Cohorts																									
Cycle (28-day cycles) except for Cycle 1 (35 days)		1								2					3			4			5			6+	
Cycle day	SC	1	2	8	11	15	22	23	29	1	2	8	15	22	1	2	15	1	2	15	1	15	1	15
Visit window (days)	-30	None	±1	±2						±1	±2													
Assessments																								
Serum uric acid, phosphorous[b]	X	X	X	X		X	X		X															
Haptoglobin, D-dimer, thrombin time and plasma fibrinogen[b]	X	X	X	X		X	X																	
PT/INR, aPTT[b]	X			X																				
Type and screen (ABO/Rh), DAT, phenotyping/ genotyping[v]	X																							
Lymphocyte subset[e]		X								X					X			X			X		X	
Peripheral blood CD20+ enumeration[f]		X								X					X			X			X		X	
Urinalysis[b]	X																							
Correlative studies[g]		X				X				X					X									
Pharmacokinetics[h]		X		X		X				X			X		X			X			X[i]		X	
Anti-drug antibodies		X								X					X						X[i]		X	
ECOG performance status	X	X		X		X	X			X					X			X			X		X	

Examination	Chemotherapy Combination (Magrolimab + R-GemOx): Phase 1b Schedule of Assessments, Safety Dose-Escalation and Expansion Cohorts																								
Cycle (28-day cycles) except for Cycle 1 (35 days)		1								2					3			4			5		6+	
Cycle day	SC	1	2	8	11	15	22	23	29	1	2	8	15	22	1	2	15	1	2	15	1	15	1	15
Visit window (days)	-30	None	±1	±2						±1	±2													
Assessments																								
Vital signs[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X	X	X	X
Physical examination[k]	X	X[c]		X	X	X	X	X	X	X			X		X		X	X			X		X	
ECG[l]	X	X		X	X					X	X													
Tumor/lymph node biopsy, mandatory[m]	X											X												
Diagnostic imaging and response assessment	X														X[n]						Q2C			
Bone marrow biopsy[o]	X														X									
Adverse events[p]																								
Concomitant medications[p]																								
Allopurinol 300 mg oral daily[q]																								
G-CSF prophylaxis[r]																								

Examination	Chemotherapy Combination (Magrolimab + R-GemOx): Phase 1b Schedule of Assessments, Safety Dose-Escalation and Expansion Cohorts																								
Cycle (28-day cycles) except for Cycle 1 (35 days)		1								2					3			4			5		6+	
Cycle day	SC	1	2	8	11	15	22	23	29	1	2	8	15	22	1	2	15	1	2	15	1	15	1	15
Visit window (days)	-30	None	±1	±2						±1	±2													
Assessments																								
Study drug administration																								
Rituximab[s]				X[s]		X	X		X	X					X			X			X		C6, then Q2C	
Magrolimab[s,t]		X		X[s]	X[t]	X	X		X	X		X	X	X	X		X	X		X	X	X	X	X	X
Gemcitabine					X			X			X		X			X	X		X	X				
Oxaliplatin					X			X			X		X			X	X		X	X				

Abbreviations: ABO = any of the four blood groups A, B, AB, and O; ADA = anti-drug antibody; aPTT = activated partial thromboplastin time; C = cycle number; CBC = complete blood count; CR = complete response; DAT = direct antiglobulin test; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; G-CSF = granulocyte colony stimulating factor; PT/INR = prothrombin time/international normalized ratio; PE = physical examination; PI = Principal Investigator; PK = pharmacokinetics; PR = partial response; Q2C = every 2 cycles; RBC = red blood cell; R-GemOx = rituximab, gemcitabine, and oxaliplatin; Rh = Rhesus factor; SC = screening.

a. First dose of magrolimab must be given within 30 days of signing informed consent.
b. Pre-infusion assessments tests may be collected up to 72 hours before study drug administration during the initial dose; however, with subsequent doses, pre-infusion assessments may be collected up to 24 hours before study drug administration.
c. May use screening pregnancy test performed within 72 hours of first dose.
d. Peripheral blood smear slides will be read locally for results and retained. Details are provided in Section 7.3.7.
e. Lymphocyte subset analysis every cycle for Cycle 1 to Cycle 6, prior to administration of study drug; following Cycle 6, analyses are at the discretion of the PI.
f. For sites that have the capability of local CD20+ testing, CD20+ B lymphocyte cell enumeration in the peripheral blood every cycle for Cycle 1 to Cycle 6, prior to administration of study drug; following Cycle 6, analyses are at the discretion of the PI. CD20+ B-cell enumeration at safety follow-up visit. Both absolute and % of lymphocytes are preferred.

g. Time point details for correlative studies are provided in Table 7-4.
h. Time point details for PK time points are provided in Table 7-3.
i. Starting with Cycle 5, samples to be collected Cycle 5 Day 1, Cycle 9 Day 1, Cycle 13 Day 1, then discontinue until safety follow-up.
j. Prior to infusion of study drug. Details are provided in Section 7.3.2.
k. Full PE at screening, symptom-directed PE thereafter. A neurologic examination should be done at minimum of Day 1 of each cycle as part of the physical examination.
l. Single at screening. For Phase 1b Dose Escalation cohort, triplicate ECGs will be performed within 2 hours prior to the first drug infusion and within 30 minutes after the last drug infusion (Section 7.3.3). This includes Cycle 1 Day 1 when only magrolimab is administered and continues through Cycle 2 Day 2. For patients enrolled in the 20-patient expansion cohort, only a single ECG at screening will be performed.
m. Two tumor/lymph node biopsies are mandatory during the study, one within the screening period and a second on-treatment (Cycle 2 Day 8, -1 to +3 weeks) unless determined to not be feasible by the Investigator. For patients who achieve a PR or CR, CCI [redacted]. For core biopsies, in addition to a specimen that is sent to the central laboratory, local lymphoma immunophenotyping panel is requested (see Appendix I). For large excisional biopsy, a portion of the specimen is to be sent for local lymphoma immunophenotyping panel, and the remainder of the tissue is to be processed and sent to central laboratory per tissue collection guidance.
n. Response assessments at Cycle 3 Day 1 (± 7 days) and then Q2C (± 7 days). Assessments may be adjusted by ± 4 weeks to coordinate with treatment cycle timing. For patients who continue on study medications for ≥18 months, response assessment may be extended to every 3 to 4 cycles at the discretion of the Investigator. Details are provided in Section 7.3.5.
o. Bone marrow biopsy will be performed for response assessment in those patients with known bone marrow disease involvement and also performed to confirm CR at any response assessment, where clinically appropriate, and at disease progression.
p. To be assessed at each physician visit.
q. Allopurinol is administered for Cycle 1 only to prevent tumor lysis syndrome. For renal impairment, 100 mg oral may be given.
r. G-CSF primary prophylaxis must be administered with gemcitabine and oxaliplatin treatment. Local standard of care or equivalent will be administered in accordance to local institutional guidelines or Investigator guidance. G-CSF prophylaxis should generally occur within several days after administration of each day gemcitabine and oxaliplatin is dosed. However, the timing of G-CSF prophylaxis may be given in accordance to local institutional guidelines.
s. On Cycle 1 Day 8 only, magrolimab should be given prior to rituximab. All other times when magrolimab and rituximab are given on the same visit, rituximab should be given before magrolimab. There should be at least an hour interval between the end of infusion of the first drug and the beginning of infusion of the second drug.
t. Cycle 1 Day 11 magrolimab Dose Escalation cohort only. Cycle 1 Day 11 magrolimab is not given to Dose Expansion cohort as of Amendment 9.
u Within 24 hours prior to each of the first 2 doses of magrolimab infusion during initial treatment (Days 1 and 8), all patients must have a documented hemoglobin $\geq$ 9.0 g/dL. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet 9.0 g/dL prior to each of the first 2 doses of magrolimab. An additional hemoglobin must be checked 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment (Days 1 and 8). The patient should be transfused as clinically appropriate. Investigators should consider additional hemoglobin monitoring during the first week of treatment in patients with symptoms of anemia or at increased risk for complications of anemia.
v ABO/Rh type, antibody screen, DAT, and extended RBC phenotyping (including minor antigens such as CcDEe, Cw, MNSs, Kk, FyaFyb, and JkaJkb) will be performed for each patient. RBC genotyping instead of extended RBC phenotyping is acceptable for any patient. A RBC genotyping (instead of an extended RBC phenotyping) must be performed if a patient received any RBC or whole blood transfusion within the previous 3 months (unless laboratory has availability for special techniques for performing phenotyping for patients with recent transfusion).

7.2. Screening Assessments

The following procedures are to be completed during the screening period:

- Confirmation that the ICF has been signed and consent process has been documented.
- Confirmation that all inclusion/exclusion criteria have been met.
- Demographic data including sex, date of birth, age, race, and ethnicity.
- Vital signs: blood pressure, heart rate, respiration, temperature, height and weight.
- Physical examination (complete) and ECOG (Appendix D).
- Single electrocardiogram (ECG).
- Evaluation for presence of B cells for DLBCL Phase 2 Cohort 4.
- Relevant medical and cancer history will be completed through consent (all findings recorded on the medical history eCRF.
- Documentation of concomitant and prior medications.
- AEs related to Screening procedures and any SAE reporting.
- Reporting of AEs caused by a protocol-mandated intervention (e.g., AEs related to invasive procedures such as biopsies)
- Urine or serum pregnancy test (in WOCBP).
- Local laboratory values, including hematology, serum or plasma chemistry, and urinalysis (Table 7-6).
- Local laboratory type and screen (ABO/Rh) and DAT (details are provided in Section 6.2.1.3 and Section 7.3.4).
- Local laboratory Peripheral Blood Smears (details are provided in Section 7.3.7).
- Tumor/lymph node biopsy: mandatory for the chemotherapy combination (magrolimab + R-GemOx) Phase 1b cohort and antibody combination (magrolimab + rituximab) Phase 2 cohort.
- Bone marrow biopsy for patients with known disease involvement of the bone marrow, prior to treatment: mandatory for all cohorts.
- Diagnostic imaging (Historic imaging may be used for screening if performed

within 30 days of the first dose of magrolimab. Details are provided in Section 7.3.5).

Screening assessments will be completed within a 30-day screening period prior to the enrollment. Patients may qualify for enrollment at any time during the 30-day screening period. Assessments performed as part of standard of care prior to ICF signature may be used if they are within the required screening period.

7.3. Description of Study Procedures

Study procedure timing is provided in Section 7.1, Schedules of Assessments.

7.3.1. Physical Examination

A complete physical examination should be performed at Screening. Thereafter, symptom-directed physical examinations are acceptable and should also include routine examination of the skin (including fingers, toes, and ears) and CNS.

7.3.2. Vital Signs

Vital signs should include heart rate, respiratory rate, blood pressure, and temperature. Height should be recorded during Screening. Weight should be recorded during Screening and on Day 1 of each cycle. Vital signs should be obtained prior to infusion of each study drug and as needed, at the investigator's discretion.

7.3.3. Electrocardiograms

One ECG will be performed at screening for all cohorts. Triplicate ECGs will be performed before the rituximab dose (within 2 hours of infusion) and within 30 minutes after the end of magrolimab infusion for the antibody combination (magrolimab + rituximab) Phase 1b cohorts only and chemotherapy combination (magrolimab + R-GemOx) for Phase 1b Dose-Escalation cohort only at designated study days.

7.3.4. Type and Screen and Direct Antiglobulin Test

Magrolimab may interfere with RBC phenotyping due to expected coating of the RBC membrane. Due to the risk of developing anemia, and because magrolimab may make phenotyping difficult, ABO/Rh type, antibody screen, blood phenotyping or genotyping, and DAT need to be performed at screening before exposure to magrolimab, as described in Section 6.2.1.3.

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

7.3.5. Diagnostic Imaging

Appropriate cancer staging assessments should be performed (e.g., fluorodeoxyglucose [FDG] positron emission tomography/computed tomography [PET/CT] for patients with lymphoma). Imaging assessments should be conducted according to Lugano Classification and LYmphoma Response to Immunomodulatory Therapy Criteria (LYRIC Criteria for lymphomas) (Table 10-1 and Table 10-2), when appropriate. The same imaging modality used at screening should be used throughout the study whenever possible. It is understood that some circumstances may require a different imaging modality. An alternate imaging modality is acceptable and may be performed at the Investigator's discretion. All scans for tumor assessments performed during the study will be sent to the imaging central laboratory designated by the Sponsor for archival.

7.3.6. Pregnancy Test

Pregnancy tests are required only for WOCBP (excluding patients who are post-menopausal with absence of menses for at least 1 year and/or surgically sterilized). A urine or serum pregnancy test is required at screening and within 72 hours before administration of magrolimab on Day 1. The Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was performed within the 72 hours before administration of magrolimab. Pregnancy tests will be performed Q4W.

7.3.7. Peripheral Blood Smear Assessment

Peripheral smears will be collected prior to selected study drug infusions and assessed for the presence or absence of RBC fragments/schistocytes and RBC agglutination, in addition to standard cell morphology assessment. These samples should be collected from the arm contralateral to the arm being used for study drug infusion/injection, if possible. All other observed findings should be reported according to local laboratory hematopathology standard procedures. Peripheral smears will be assessed locally per the guidelines provided in Appendix E.

7.3.8. Adverse Events

After signing of informed consent, but prior to initiation of study medications, only events deemed by the Investigator to have been caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies) will be collected as AEs or SAEs, if applicable (Section 9.2.1).

After the first dose of study drug, all AEs observed by the Investigator or reported by the patient after the first dose of any of the study drugs through 30 days after the discontinuation of study treatment, are to be reported using the applicable eCRF (Section 9).

Following 30 days after the last dose of investigational product, Investigators should only report any SAEs that are considered to be related to study treatment (magrolimab, rituximab, gemcitabine, and/or oxaliplatin).

7.3.9. Concomitant Medications

All concomitant medications taken by a patient while on study are to be documented. Changes in baseline concomitant medication information is to be collected after consent through the end of 30-day Safety Follow-up Period. Concomitant medication associated with procedure-related events will be captured from the time of informed consent on. Information to be collected includes therapy name, indication, dose, unit, frequency, route, start date, and stop date, and are to be reported using the applicable eCRF.

7.4. Safety Follow-up Visit

The Safety Follow-up visit is to be completed 30 days ± 7 days after the last dose of magrolimab, rituximab, gemcitabine, and/or oxaliplatin or prior to beginning a new anti-cancer therapy, whichever is earlier. Reason for discontinuation of study treatment will be recorded.

- Local laboratory
  - CBC (with differential, platelets, retics)
  - Serum or plasma chemistry
- Serum or urine pregnancy test (in WOCBP)
- PK sample collection. Separate PK samples will be collected for magrolimab and rituximab.
- ADA testing
- ECOG performance status (Appendix D)
- Vital signs
  - blood pressure
  - heart rate
  - respiration
  - temperature
  - weight
- Physical examination (symptom-directed)
- Diagnostic imaging (± 7 days), if not performed within the last 4 weeks (Section 7.3.4)
- Response assessment (± 7 days), if not performed within the last 4 weeks (refer to Section 10.2)
- AEs
- Concomitant medications

- Refer to the schedule provided in Table 7-2 for specific Safety Follow-up Visit procedures.
- Following the Safety Follow-up Visit, patients with ongoing SAEs and study drug-related AEs will be followed for safety. If any SAEs or study drug-related AEs are ongoing after the Safety Follow-up Visit, follow-up with the patient will occur at least Q4W until resolution (or return to baseline) or stabilization of these events, unless the patient starts a new anti-cancer treatment or until the medical monitor deems it necessary after the end of the study. Follow-up will stop when apatient begins a new anti-cancer treatment.

7.5. Safety Assessments

Analytes to be assessed by the local laboratory or specialty laboratories are presented in Table 7-6.

Table 7-6 Laboratory Analyte Listing for Safety and Other Assessments

Chemistry	Hematology	Urinalysis	Type and Screen (ABO/Rh), Direct Antiglobulin Test	Other Laboratory Measurements
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine Uric acid Phosphorus Total bilirubin Direct bilirubin LDH AST (SGOT) ALT (SGPT) Alkaline phosphatase	RBC Hemoglobin Hematocrit Platelets WBC Differential • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes Reticulocytes Haptoglobin D-Dimer Thrombin Plasma fibrinogen PT, aPTT, and INR Peripheral Blood Smear • Spherocytes • RBC Fragments/Schistocytes • RBC Agglutination • Nucleated RBCs • RBC abnormalities • Platelet Aggregation Lymphocyte subset analysis • CD20+ B lymphocyte cell enumeration in the peripheral blood	RBC Glucose Protein Urine pH Ketones Bilirubin Urine Specific gravity Blood	ABO Rh Blood Group System • Rh D Factor • Rh C Factor • Rh E Factor • Rh c Factor • Rh e Factor Phenotyping/genotyping (including minor antigen such as CcDEe, Cw, MNSs, Kk, FyaFyb, JkaJkb) Antigen MNS Blood Group • M +/- • N +/- • S +/- • s +/- DAT	Serum or Urine Pregnancy Correlative studies Pharmacokinetics ADAs

Notes: Full phenotyping should be performed if the patient has not been transfused in last 3 months. These assays may be performed at a specialty laboratory. Refer to Section 7.1 for Schedule of Assessment tables for collection time points. Refer to Section 7.7.5 for biopsy guidelines.
Abbreviations: ABO = any of the four blood groups A, B, AB, and O; ADA = anti-drug antibody; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DAT = direct antiglobulin test; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell; Rh = Rhesus factor; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cells.

7.6. Efficacy Assessments

Patients will be assessed for response using the Lugano Classification and LYRIC Criteria for lymphomas (Table 10-1 and Table 10-2). The first response assessment will occur at Cycle 3 Day 1 (± 7 days). Subsequent response assessments will occur Q8W and may be adjusted by ± 4 weeks to coordinate with treatment cycle timing. For patients who continue on study medication(s) for ≥18 months, response assessment may be extended to every 3 to 4 cycles at the discretion of the Investigator. Response assessment will be obtained at treatment termination, unless a prior radiographic assessment has been performed within the last 7 days or at a prior response assessment that documented progressive disease.

For patients with disease involvement in the bone marrow prior to treatment, a bone marrow aspirate and biopsy will be performed at first response assessment on Cycle 3 Day 1. In addition, a bone marrow assessment will be conducted to confirm CR, which may occur at any response assessment time point. If a patient achieves a CR, subsequent bone marrow aspirate and biopsies are not required to be performed, but may be performed at the Investigator's discretion.

7.6.1. Immunogenicity

Peripheral blood for immunogenicity assessments for ADAs against magrolimab will be collected on Day 1 before infusion and then according to the SOA. When collected on the day of study drug dosing, the blood sample must be collected pre-dose. A validated assay will be used to measure antibodies to magrolimab in serum samples. Neutralizing antibodies to magrolimab may also be assessed for patients who test positive for ADA. ADAs to rituximab may be assessed if the CTSC or Sponsor determines such testing is needed.

7.7. Pharmacodynamic and Biomarker Assessments

7.7.1. CD47 Receptor Occupancy

Testing for CD47 RO on select target cells enables PD testing of magrolimab to

inform both safety and efficacy parameters. First, the degree of saturation of CD47 receptors on RBCs serves as a PD assessment for degree of anemia. Second, CD47 RO on WBCs and circulating or bone marrow-resident lymphoma cells provides information on the level of CD47 saturation of the internal CD47 tissue sink and drug exposures on tumor cells, respectively.

In settings in which there is disease involvement of the bone marrow, a bone marrow aspirate sample will be obtained on Cycle 3 Day 1 (± 7 days) for response assessment, and will be used to assess CD47 RO in the bone marrow, additional correlative study assessments, and biobanking.

The RO sample collection in peripheral blood was discontinued in Protocol Amendment 6. At the discretion of the Sponsor, CD47 RO studies may not be performed at clinical sites where sample shipments cannot be delivered within stability time parameters (due to transit times). At the discretion of the CTSC, CD47 RO studies may be discontinued if sufficient data have been collected.

CD47 RO is not currently being conducted in the chemotherapy combination (magrolimab + R-GemOx) cohort but may be added in at the discretion of the CTSC based on emerging data.

7.7.2. Correlative Blood Samples

Correlative studies will be performed on peripheral blood samples to determine the biologic activity of magrolimab in combination with rituximab or R-GemOx on circulating immune cells and molecular subtypes of NHL. These studies may include, but are not limited to, investigations of plasma cytokine levels, characterization of circulating T cells, characterization of circulating tumor or cell-free deoxyribonucleic acid (DNA) and other studies. Where applicable, blood samples will be collected according to the schedule presented in Table 7-4. If at any point in the study the CTSC determines that sufficient correlative data have been generated, it may halt the collection and analysis of these samples.

7.7.3. Measurement of Plasma Cytokines

Cytokine release by immune cells is one surrogate measure of immune cell activation (including T cells and macrophages). Since magrolimab activates both macrophages and T cells, it is hypothesized that a specific cytokine profile relating to immune cell activation will correlate with clinical response to therapy. The platform allows for a high-throughput analysis of a multitude of cytokines and chemokines with high sensitivity (Swartzman 1999). This predefined multiplex panel of human cytokines will be measured from a small thawed vial of plasma, detecting and quantifying the soluble proteins and peptides which help control cellular function.

The observed systemic biochemical changes in the blood may provide a further correlate with tumor progression and therapeutic response and help provide a much broader understanding of disease. A specific focus on cytokines involved in macrophage, dendritic cell, and T-cell activation/repression will be explored given the nonclinical mechanism for magrolimab to engage these immune cells.

7.7.4. Characterization of Circulating T Cells

In nonclinical studies, macrophage-mediated phagocytosis of tumor cells by an anti-CD47 antibody leads to cross-presentation of antigens and subsequent T-cell activation (Tseng 2013). It is therefore predicted that magrolimab administration may lead to T-cell activation in patients. Peripheral blood samples will be collected and T-cell activation/repression markers/studies may be performed on CyTOF, in vitro T-cell activation assays, and T-cell receptor sequencing.
Additional peripheral blood mononuclear cells, serum, and plasma at the specified time points will also be cryopreserved and biobanked for future analyses.

7.7.5. Tumor and Bone Marrow Biopsies

Tumor and bone marrow biopsies will be collected to investigate lymphoma

immunophenotyping, study drug modulation of the tumor environment, penetration into the tumor, and correlation of anti-cancer response to molecular subtypes of NHL. Analysis of immune cell composition within these tumor samples will be performed by IHC, immunofluorescence, or other similar assay to include macrophage, lymphocyte, and other immune cell subsets. Markers of immune cell activation may also be investigated by flow cytometric analysis or other similar method, in addition to frequency of immune cell infiltrates within the tumors. It is hypothesized that higher levels of macrophage and/or T-cell infiltration in the tumor either pretreatment or post-treatment will correlate with a clinical response to therapy.

From the tumor biopsies obtained according to Section 7.1, detection of the presence of study drug (magrolimab and/or rituximab) saturation in tumors will be determined. Saturation of tumor cells with magrolimab and/or rituximab will be determined by measuring levels of magrolimab, human IgG4, and/or anti-rituximab antibodies. Analysis of magrolimab penetration into tumor tissue will be analyzed in paired treatment biopsies obtained from study patients. The proportion of patients with magrolimab presence in tumor tissues as measured by IHC (1+ or greater) will be calculated for each expansion cohort independently, and the 95% confidence intervals (CI) for each will be determined.

From the same tumor biopsies, DNA/ ribonucleic acid (RNA) sequencing may be performed to assess for genomic mutations, gene expression changes, cell-of-origin status, and presence of neoantigens pre and post initiation of therapy. Paired peripheral blood samples may also be used for sequencing to aid in determining germline status. Remaining tumor samples at the specified time points may be cryopreserved and biobanked for future analyses.

CCI [redacted] Likewise, tumor biopsies are mandatory for the antibody combination

(magrolimab + rituximab) Phase 2 cohort, unless the Investigator determines that it is not feasible. Reasons for biopsy not being feasible could include, but are not limited to, lack of accessible tumor tissue to biopsy and patient safety issues. A tumor (lymph node) biopsy will be obtained during the screening period and on Cycle 2 Day 8 (-1 week to +3 weeks). Core biopsies will be collected at these time points. Where possible, excisional biopsies are preferred over core biopsies. Archival tumor tissue block may be collected by the Sponsor for correlative studies. The tissue block is preferred, but if not available, upon Sponsor's request, at least 10 unstained slides may be sent to central laboratory.

In cases in which there is known disease involvement of the bone marrow, a bone marrow aspirate and biopsy are mandatory for all cohorts and will be conducted prior to treatment and on Cycle 3 Day 1 (± 7 days) for response assessment CCI [redacted]. A separate aspirate sample is also to be collected at the same time to assess CD47 RO in the bone marrow, additional correlative study assessments, and biobanking. The bone marrow core biopsy will be sent to the CCI [redacted].

Refer to the laboratory manual for specific instruction. It may be necessary to collect a separate core biopsy from the one collected for clinical diagnosis.

In addition, for patients who achieve a PR or CR while on study, a repeat tumor biopsy and bone marrow aspirate/biopsy (where applicable) will be collected at the time of disease progression or relapse whenever possible. CCI [redacted]. At the discretion of the Sponsor, the separate bone marrow aspirate may not be performed at clinical sites where sample shipments cannot be delivered within stability time parameters (due to transit times).

8. STUDY DISCONTINUATION

8.1. Withdrawal of Patients from Study Drug Treatment

Patients (or a legally acceptable representative) may decline to continue receiving study drug at any time during the study. The patient's health and welfare is the primary consideration in any determination to discontinue study drug treatment.

It is strongly encouraged that patients to return for their Safety Follow-up Visit 30 days (± 7 days) after their last dose of study drug as outlined in Section 7.1, Schedules of Assessments. All patients who withdraw from study drug treatment will be followed for disease response and survival.

Patients who develop a known adverse reaction to rituximab, gemcitabine, and/or oxaliplatin may continue treatment with magrolimab and will not be required to discontinue the study. This continuation requires consultation with the Sponsor. Reasons for patient withdrawal from study drug treatment may include, but are not limited to, the following:

- Patient's request, with or without a stated reason
- Evidence of tumor progression
- Clinically significant deterioration of the patient's -condition including clinically significant study drug-related AEs
- AE
- Noncompliance
- Pregnancy

8.2. Withdrawal of Patients from Study

Patients have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care. Patients (or a legally acceptable representative) may decline to continue receiving study drug and/or other protocol-required therapies or procedures at any time during the study. Patient data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data may be included after withdrawal of consent.

The Investigator is to discuss with the patient the appropriate procedures for withdrawal from the study. The Investigator or Sponsor has the right to discontinue any patient from study participation.

Reasons for patient discontinuation may include, but are not limited to, the following:

- Patient's request, with or without a stated reason
- Protocol-specified reason
- Clinically significant deterioration of the patient's condition
- Noncompliance
- Sponsor's discretion
- Lost to follow-up

8.3. Study Termination

Gilead Sciences reserves the right to terminate the study at any time. Both Gilead Sciences and the Investigator reserve the right to terminate the Investigator's participation in the study according to the study contract. The Investigator is to notify the IRB/Independent Ethics Committee (IEC) in writing of the study's completion or early termination and send a copy of the notification to Gilead Sciences.

9. ASSESSMENT OF SAFETY

9.1. Safety Parameters and Definitions

Safety assessments will consist of recording all AEs and SAEs; protocol-specified hematology and clinical chemistry variables; measurement of protocol-specified vital signs, ECGs, and physical exams; and the results from other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

Gilead Sciences or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating Investigators, in accordance with International Conference on Harmonisation (ICH) guidelines, Food and Drug Administration (FDA) regulations, European Clinical Trials Directive, and/or local regulatory requirements.

9.1.1. Adverse Event

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with a patient's cancer that were not present prior to the AE reporting period (refer to Section 9.2.1)
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)
- Events that occur prior to administration of study treatment that are related to a protocol-mandated intervention (e.g., invasive procedures such as biopsies)
- Preexisting medical conditions, judged by the Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

9.1.2. Serious Adverse Event

An SAE is any AE that at any dose:

- Is fatal (i.e., the AE is the actual cause of death)
- Is Life threatening (i.e., the AE in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the study drug(s)
- Considered a significant medical event by the Investigator based on sound medical and scientific judgment (i.e., may jeopardize the patient or may

require medical/surgical intervention to prevent one of the outcomes listed above)

All AEs that do not meet any of the criteria for serious should be regarded as non-SAEs.

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (as in Grade 1 [mild], Grade 2 [moderate], Grade 3 [severe], Grade 4 [life-threatening] or Grade 5 [death] per CTCAE v. 4.03). The event itself may be of relatively minor medical significance (such as severe headache). “Serious” is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient’s life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

9.2. Methods and Timing for Capturing and Assessing Safety Parameters

The Investigator is responsible for ensuring that all AEs and SAEs are recorded on the eCRF. SAEs are reported on the SAE report form and reported to the Sponsor in accordance with protocol instructions. SAEs must be reported to the Sponsor or designee within 24 hours of the Investigator becoming aware of the event.

9.2.1. Adverse Event/Serious Adverse Event Reporting Period

After signing of informed consent, but prior to initiation of any of the study drugs, all events deemed by the Investigator to have been caused by a protocol mandated intervention (e.g., invasive procedures such as biopsies) will be collected as AEs (or SAEs if any of the serious criteria apply).

After initiation of the study drug, all AEs and SAEs, regardless of attribution, will be collected until 30 days following the last administration of study treatment or the Safety Follow up Visit (whichever is later) unless the patient begins an alternative anti-cancer therapy prior to the said period. After 30 days post-last dose of study

drug or the Safety Follow-up Contact (whichever is later), Investigators are to report only new study drug-related AEs or SAEs.

The Investigator must report any follow-up information regarding SAEs and study drug-related AEs until resolution (or return to baseline) or stabilization, unless the patient starts a new anti-cancer therapy or until the medical monitor deems it necessary after the end of the study. At any time, Investigators are to report SAEs that they assess to be related to any of the study drugs (magrolimab, rituximab, gemcitabine, and/or oxaliplatin received as part of this study).

9.2.2. Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive questions include:

> "How have you felt since your last clinic visit?"
> "Have you had any new or changed health problems since you were last here?"

9.2.3. Assessment of Severity and Causality of Adverse Events

Investigators will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF and on the SAE report form, if applicable.

For each AE and SAE, the Investigator will make an assessment of seriousness (refer to Section 9.1.2 for seriousness criteria), severity (Table 9-1), and causality. A causality assessment will be made for each of the study drugs (i.e., magrolimab and R-GemOx). Table 9-2 provides guidance for assessing the causal relationship to the study drug(s).

The AE grading (severity) scale NCI CTCAE v4.03 (Appendix B) will be used for AE reporting.

Table 9-1 Adverse Event Grade (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL.
3	Severe (apply event-specific NCI CTCAE grading criteria)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Life-threatening consequences; urgent intervention indicated.
5	Death related to adverse event	Death related to adverse event.

Source: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03.
Abbreviations: ADL = activities of daily life; AE = adverse event.
a. Use the alternative descriptions for Grade 1, 2, 3, and 4 events when the observed or reported AE does not appear in the NCI CTCAE listing.

To ensure consistency of causality assessments for any study drug, Investigators should apply the following general guidelines:

Table 9-2 Causal Attribution Guidance

Is the AE/SAE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?	
YES (Related)	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship possible, AND other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.
NO (Not Related)	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship unlikely, OR other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

Abbreviations: AE = adverse event; SAE = serious adverse event.
Note: The Investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, Gilead Sciences or its designee, will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators and applicable regulatory authorities.

9.3. Procedures for Recording Adverse Events

9.3.1. Recording Adverse Events on the eCRF

Investigators should use correct medical terminology/concepts when recording AEs and SAEs. Avoid colloquialisms and abbreviations.

A separate log line in the Adverse Event eCRF should be used for each medical concept that needs to be recorded. Causal relationship of AEs and SAEs attributed to each study drug (i.e., magrolimab and R-GemOx) should be recorded individually.

9.3.1.1. Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE on separate log lines of the eCRF and SAE report form (if the event is serious). If a diagnosis is subsequently established, it should be reported to Gilead Sciences. by subsuming the symptoms under the reported diagnosis according to the CRF Completion Guidelines.

9.3.1.2. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE on the eCRF. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

9.3.1.3. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the eCRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on a new log line on the Adverse Event eCRF indicating the change in severity.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on Adverse Event eCRF.

9.3.1.4. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities and ECG results that require active management will be recorded as AEs on the eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 $\times$ ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event eCRF.

If the laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE on the eCRF only if it is deemed clinically significant. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

9.3.1.5. Deaths

All events leading to death that occur during the protocol-specified AE reporting period (Section 9.2.1), regardless of attribution, will be recorded on an eCRF and SAE report form, and reported to the Sponsor within 24 hours of awareness and not later than the next business day.

When recording a death on an eCRF or SAE Report Form, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept, if known.

9.3.1.6. Worsening of Disease

Worsening of and/or progression of disease should not be routinely recorded as an AE or SAE if not resulting in death. These data will be captured as efficacy assessment data. However, worsening and/or progression of lymphoma should be recorded as an SAE if the outcome is fatal in the absence of other signs and symptoms (Section 9.3.1.5), or if the Investigator assesses the disease progression to be related to study treatment.

9.3.1.7. Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study
- Hospitalization for social reason (e.g., respite care, waiting for insurance authorization)

9.3.1.8. Other Reportable Information

Certain information, although not considered an AE or SAE, must be recorded, reported, and followed up as indicated below. This includes the following:

Pregnancy

Female patients who become pregnant during the study must discuss with the Investigator their treatment options and must discontinue receiving any of the study drugs immediately. Male patients whose partners become pregnant may continue receiving study treatment; however, they must use a barrier method (condom) to prevent the unborn fetus from being exposed to any of the study drug.

Any pregnancy occurring in a patient or a patient's partner during treatment with any study drug or within 6 months of last study drug administration must be reported within 24 hours of becoming aware of it, using a Pregnancy Notification Form (provided in the Investigator Trial File). If the pregnancy occurs in a patient's partner, the Investigator must obtain consent from the patient's partner before collecting any pregnancy-related information. All pregnancies must be followed up until there is a pregnancy outcome. The Investigator must report the pregnancy outcome using a pregnancy outcome form. In the event that the neonate/s has/have abnormalities at birth, additional data will be collected regarding the abnormalities.

Any congenital anomaly/birth defect in an offspring born to a patient or female partner of a male patient exposed to study drug should be recorded and reported as an SAE within 24 hours of awareness.

Stillbirth or spontaneous or therapeutic abortion must be reported as an SAE (medically significant event) and recorded on an SAE Report Form, and forwarded to the Sponsor as described in Section 9.4.1.

Overdose

An overdose is a dose higher than that indicated in the protocol, with or without an AE.

Abuse or Misuse

Abuse or misuse of a study drug is use for nonclinical reasons, with or without experiencing an AE.

9.4. Reporting Requirements for Serious Adverse Events

9.4.1. Reporting Requirements for All Serious Adverse Events

Investigators will submit reports of all SAEs, regardless of attribution, within 24 hours of awareness according to the instructions provided by the Sponsor.

9.5. Emergency Contacts

Medical Monitor Contact Information for Sites in Case of an Emergency:
email: #5f9003mm@gilead.com

10. MEASUREMENT OF EFFECT

10.1. Anti-cancer Effect – Hematologic Tumors

Both Lugano Classification and LYRIC Criteria will be used for evaluation of response. The first response assessment will occur at Cycle 3 Day 1 (± 1 week). Subsequent response assessments will occur Q8W (± 1 week). For patients who continue on study medication(s) for ≥18 months, response assessment may be decreased to every 3 or 4 cycles at the discretion of the Investigator. Response assessment will be obtained at treatment termination, unless a prior radiographic assessment has been performed within the last 7 days or at a prior response assessment that documented progressive disease. Definitions of response parameters are provided below. For patients with disease involvement in the bone marrow prior to treatment, a bone marrow aspirate and biopsy will be performed at the first response assessment at the beginning of Cycle 3. In addition, a bone

marrow assessment will be conducted to confirm CR, which may occur at any response assessment time point. If a patient achieves a CR, subsequent bone marrow aspirate and biopsies are not required to be performed, but may be performed at the Investigator's discretion.

10.2. Evaluation of Response

Hematologic tumor response will be evaluated using Lugano Classification, reproduced from Cheson 2014, outlined in Table 10-1 below. Immune response will be evaluated using the LYRIC criteria reproduced from Cheson 2016, outlined in Table 10-2.

Table 10-1 Lugano Classification of Response in Non-Hodgkin's Lymphoma

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extra lymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following):
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 x 0 mm
		For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase

Response and Site	PET-CT–Based Response	CT-Based Response
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable

Response and Site	PET-CT–Based Response	CT-Based Response
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following PPD progressions:
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	An individual node/lesion must be abnormal with LDi > 1.5 cm and
Extranodal lesions	New FDG avid foci consistent with lymphoma at interim or end of treatment assessment.	Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation) If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis, if 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

Footnotes: *A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters.

Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation.

Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but arestill considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging.

In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growthfactors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma. Source: Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin's lymphoma: the Lugano Classification. J Clin Oncol. 2014;32(27):3059-3068 (Cheson 2014); refer also to Appendix C.

If a patient's response is PD based on LUGANO Classification and has indeterminant response (IR) per LYRIC Criteria, then the patient may continue on the study treatment unless there is disease progression according to LYRIC Criteria.

For patients staged with PET/CT focal uptake in nodal and extranodal sites that is in keeping with lymphoma, according to the distribution and/or CT characteristics, is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on. For patients staged with CT, up to 6 of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in 2 diameters (longest diameter [LDi] and shortest diameter) should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved. A measurable node must have an LDi greater than 1.5 cm. Measurable extranodal disease (e.g., hepatic nodules) may be included in the 6 representative, measured lesions. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as non-target disease (e.g., cutaneous, gastrointestinal, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites). In patients in whom a discordant histology or malignant transformation is suspected, a PET/CT may identify the optimal site to biopsy for confirmation.

The following modifications to the Lugano Classification will be made for this study protocol:

Bone marrow assessment: For patients with disease involvement of the bone marrow prior to treatment, a bone marrow aspirate and biopsy will be performed at first response assessment at the beginning of Cycle 3. In addition, a bone marrow assessment will be conducted to confirm CR, which may occur at any response assessment time point. If a patient achieves a CR, subsequent bone marrow aspirate and biopsies are not required to be performed, but may be performed at the Investigator's discretion.

Refinement of the Lugano Classification, LYRIC Criteria: Based on emerging

data in immunomodulatory agents, of which magrolimab is one, it appears that these agents may be associated with clinical and imaging findings during treatment suggestive of progressive disease, despite evidence of clinical benefit.

Thus, according to the LYRIC Criteria, an indeterminate response (IR) criteria will be utilized for response assessment. A patient will be considered to have IR in 1 or more of the 3 following circumstances:

1. Increase in overall tumor burden (as assessed by sum of the product of the diameters [SPD]) of ≥ 50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration [IR(1)]
2. Appearance of new lesions or growth of one or more existing lesion(s) ≥ 50% at any time during treatment; occurring in the context of lack of overall progression (< 50% increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during the treatment [IR(2)]
3. Increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size or number [IR(3)]

For patients categorized as having any of the above types of IR, it is mandatory to obtain a repeat imaging after an additional 12 weeks (or earlier if clinically indicated). At that time, response should be re-evaluated, and the patient should be considered to have true progressive disease if the SPD of target lesion has increased further, with the considerations below:

- In the case of IR(1), the comparison should be between the first IR(1) and the current SPD, with an increase of ≥ 10% constituting progressive disease. In addition, there should be an increase of ≥ 5 mm (in either dimension) of ≥ 1 lesion for lesions ≤ 2 cm and 10 mm for lesions > 2 cm, to be consistent with the Lugano classification. The 10% threshold is empiric, but designed to account for variability in measurement, particularly when taken along with the minimum increase. If the target SPD increase is < 10%, the response would still be categorized as IR(1), and the patient could continue treatment until a subsequent scan shows either true progressive disease [≥ 10% increase from

first IR(1) time point and an increase of > 5 mm in either dimension of ≥ 1 lesion] or response (≥ 50% decrease from baseline). In this situation, it is reasonable to repeat imaging in 4 to 8 weeks of the original IR(1) time point to ensure absence of significant further increase.

- In the case of IR(2), the new or growing lesion(s) (unless biopsy proven to be benign) should be added to the target lesion(s), up to a total of no more than 6 total lesions. If the SPD of the newly defined set of target lesions has increased ≥ 50% from their nadir value (which may precede the IR time point), the patient should be considered to have progressive disease.
- In the case of IR(3), because inflammatory responses may result in an increase in the standardized uptake value of a lesion, the patient will not be considered to have progressive disease unless there is evidence of progressive disease by an increase in lesion size or the development of new lesions, as noted above.

A comparison of Lugano Classification and LYRIC Criteria is provided in Table 10-2.

Table 10-2 Comparison of Lugano Classification and LYRIC Criteria

Criteria	CR	PR	PD
Lugano	PET-CT, score 1, 2, or 3* with or without a residual mass on 5PS† OR on CT, target nodes/nodal masses must regress to ≤1.5 cm in LDi	PET-CT score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size. OR On CT ≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites	PET-CT score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end- of-treatment assessment. OR On CT, an individual node/lesion must be abnormal with: LDi >1.5 cm and increase by ≥50% from PPD nadir and an increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm
			In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by ≥2 cm from baseline. New or recurrent splenomegaly
			New or clear progression of preexisting nonmeasured lesions
			Regrowth of previously resolved lesions A new node >1.5 cm in any axis or a new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma
			AND/OR new or recurrent involvement of the bone marrow

Criteria	CR	PR	PD
LYRIC	Same as Lugano	Same as Lugano	As with Lugano with the following exceptions: IR IR(1): ≥50% increase in SPD in first 12 weeks IR(2): <50% increase in SPD with: a. New lesion(s), or b. ≥50% increase in PPD of a lesion or set of lesions at any time during treatment IR (3): increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD.

Abbreviations: 5PS = 5-point scale; CR = complete response; CT = computed tomography; FDG = fluorodeoxyglucose; IR = indeterminate response; LDi = longest diameter; LYRIC = LYmphoma Response to Immunomodulatory Therapy Criteria; PD = pharmacodynamics(s); PET = positron emission tomography; PPD = product of the perpendicular diameters; PR = partial response; SDi = short diameter; SPD = sum of the product of the perpendicular diameters for multiple lesions.
*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake greater than liver; 5, uptake markedly higher than liver (2-3 times SUVmax in normal liver) and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Source: This is an excerpt from: Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood. 2016;128(21):2489-2496. (Cheson 2016); refer also to Appendix C.

10.2.1. Assessment of Evaluable Rather Than Measurable Disease

Patients with evaluable, but not measurable response, will be assessed with the study used to establish evaluable disease at least Q8W.

11. STATISTICAL CONSIDERATIONS

11.1. Analysis Sets

Enrolled Analysis Set – includes all enrolled patients. Typically, summary tables of disposition and protocol deviations will be performed on the Enrolled Analysis Set.

DLT Analysis Set 1 (Antibody Combination [magrolimab + rituximab]) – includes all enrolled Phase 1b patients in the magrolimab + rituximab cohort who met EITHER of the following criteria:

- The patient experienced a DLT
- The patient completed at least 3 infusions of magrolimab and 2 infusions of rituximab.

DLT Analysis Set 2 (Chemotherapy Combination [magrolimab + R-GemOx]) – includes all enrolled Phase 1b patients in the magrolimab + R-GemOx cohort who met EITHER of the following criteria:

- The patient experienced a DLT at any time after initiation of the first infusion of magrolimab, rituximab, and gemcitabine or oxaliplatin
- The patient completed at least 3 infusions of magrolimab, 2 infusions of rituximab, and 1 infusion of gemcitabine and oxaliplatin

Efficacy Analysis Set (EAS) – includes all enrolled patients who received at least 1 dose of magrolimab.

The analyses of ORR, DOR, progression-free survival (PFS), OS, and TTP will be performed on the EAS.

Safety Analysis Set (SAF) – includes all enrolled patients who receive at least 1 dose of any study drug.

Safety, demographics, and medical/cancer history, etc., will be performed on the SAF.

Pharmacokinetics Analysis Set – includes all patients who receive at least 1 dose of study drug and have measurable concentrations of magrolimab from PK blood samples.

11.2. Sample Size Determination

The overall sample size for both the antibody combination (magrolimab + rituximab) and chemotherapy combination (magrolimab + R-GemOx) cohorts can be up to 422 patients.

11.2.1. Antibody Combination (Magrolimab + Rituximab)

The overall sample size could be up to 354 for enrollment of the antibody combination (magrolimab + rituximab) cohort to ensure sufficient efficacy-evaluable patients for each indication. This sample size includes both the Phase 1b and Phase 2 parts of the antibody combination (magrolimab + rituximab). In the Phase 1b antibody combination (magrolimab + rituximab) cohort of the study, a standard 3+3 dose escalation design is employed to explore the MTD of the investigational combination. There were 4 dose cohort levels, with an estimated total of 25 to 38 patients planned in the Phase 1b depending on the possible cohort expansion in a 3+3 design. In Phase 1b, patients who were not evaluable for DLT were to be replaced. The Phase 2 part of the study will enroll patients with indolent lymphoma or DLBCL. Pending decisions from CTSC, additional arms in Phase 2 may be opened to test dose levels different from the current RP2DS of 30 mg/kg.

Cohorts 1 to 3 of the antibody combination (magrolimab + rituximab) Phase 2 part of the study will comprise up to 216 patients evaluable for efficacy (up to 94 with indolent lymphoma and 94 with DLBCL) if both stages of each group are fully accrued. The additional 28 patients account for testing of additional dose regimens for indolent lymphoma and DLBCL. The sample size of 94 was determined to

ensure the lower bound of the 95% CI will exclude 30% if the observed response rate is 40% or higher.

Cohort 4 of the antibody combination (magrolimab + rituximab) Phase 2 part of the study will comprise up to 100 DLBCL patients if both stages are fully accrued. The sample size of 100 was determined to ensure the lower bound of the 95% CI will exclude 20% if the ORR is 30% or higher. This desired ORR is based on a ORR that is higher than current standard of care and that provides significant clinical benefit for these DLBCL and indolent lymphoma heavily pretreated patient populations.

11.2.2. Chemotherapy Combination (Magrolimab + R-GemOx)

The total planned number of patients for the chemotherapy combination (magrolimab + R-GemOx) Phase 1b cohort is 29 to 68 efficacy-evaluable patients, including the safety dose-escalation cohort of approximately 9 to 48 patients (if dose de-escalation occurs an additional 6 patients may be enrolled for 2 dose levels) and the expansion of approximately 20 patients.

For the chemotherapy combination (magrolimab + R-GemOx) Phase 1b cohort, an initial safety dose escalation will be conducted. If the treatment combination is not tolerated, dose de-escalation of magrolimab may occur with another 6 patients across two dose levels treated in the safety phase. If the magrolimab + R-GemOx regimen is well-tolerated, an additional 20 patients will be treated in an expansion phase to determine efficacy. The sample size of 26 total efficacy-evaluable patients was calculated based on a desired ORR of ≥50% for the treatment combination. With a sample size of 26 patients, the lower bound of the 95% CI would exclude an alternative ORR of 33%. A 33% ORR is what has been reported for R-GemOx in the indicated DLBCL population (Mounier 2013) with a desired ORR of ≥50% in the chemotherapy combination (magrolimab + R-GemOx) Phase 1b cohort is expected to provide a meaningful clinical improvement and benefit in this patient population.

11.3. Statistical Analyses Methods

All analyses will be conducted for the antibody combination (magrolimab + rituximab) cohorts, including Phase 1b, Phase 2, and combined, unless otherwise specified. Allanalyses will be conducted for the chemotherapy combination (magrolimab + R-GemOx) cohort, unless otherwise specified.

For continuous variables, the mean, standard deviation (SD), median, and ranges will be provided. For categorical variables, the frequency and percentage in each category will be provided, along with 95% CIs, when appropriate. For time-to-event variables, the Kaplan-Meier (KM) estimates (unit: month) and corresponding two-sided 95% CIs for the median and quartiles will be provided. The KM plot may also be provided. Details regarding the statistical analysis to be conducted, including the handling of missing data and patient withdrawal, will be provided in the Statistical Analysis Plan (SAP).

11.3.1. Efficacy Analyses

Endpoints used in the efficacy analysis are ORR, DOR, PFS, OS, and TTP.

11.3.1.1. Objective Response Rate

Objective response is defined as CR+PR determined by Lugano Classification (primary efficacy) and LYRIC criteria (secondary efficacy) for lymphomas (Table 10-1 and Table 10-2). ORR is defined as the proportion of patients with objective response in the EAS.

11.3.1.2. Duration of Response

The DOR is measured from when the first (objective) response is met (i.e., CR or PR) until the first date of objectively documented progressive disease. Patients who do not have objectively documented progressive disease will be censored at the last response assessment date with evidence of no disease progression/relapse.

11.3.1.3. Progression-free Survival

The PFS is measured from dose initiation until the first date of objectively documented disease progression or death, whichever occurs earlier. Patients who do not have objectivelydocumented disease progression AND not died will be censored at the last response assessment date with evidence of no disease progression/relapse.

11.3.1.4. Overall Survival

The OS is measured from dose initiation until death. Patients who did not die will be censored at their last known alive date.

11.3.1.5. Time to Progression

The TTP is measured from dose initiation until the first date of objectively documented progressive disease. Patients who do not have objectively documented progressive disease (in the response evaluation form of the eCRF) will be censored at the last response assessment date with evidence of no disease progression/relapse.

11.3.2. Pharmacokinetics/Pharmacodynamics Analyses

11.3.2.1. Pharmacokinetic Analyses

The PK analysis will be conducted for magrolimab and possibly, rituximab on the PK Analysis Set. Based on the distinct MOAs of magrolimab and rituximab, overlapping drug PK interactions are not expected. For the chemotherapy combination (magrolimab + R-GemOx) cohort, overlapping drug PK interactions are not expected for magrolimab and R-GemOx. Thus, samples for PK analysis for rituximab for all cohorts will be banked and will be conducted based on CTSC recommendation. Thus, samples for PK analysis for magrolimab for all cohorts will be banked and will be conducted based on CTSC recommendation. Individual patients may be removed from the estimation of particular PK parameters based on the number of available blood samples for them. These patients will be identified at the time of analysis.

With the frequency of dosing and sampling in mind, the following parameters may be calculable after single and multiple doses (Table 11-1).

Table 11-1 Noncompartmental Pharmacokinetic Parameters

AUC_{last}	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass × time × volume - 1)
AUC_{tau}	The AUC calculated to the end of a dosing interval (tau) at steady state (amount × time × volume - 1)
C_{max}	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass × volume - 1)

The PK parameters listed in Table 11-1 will be determined using non-compartmental method(s) for magrolimab.

All concentrations that were BLQ or missing data will be reported as such in the concentration data listings. The BLQ concentrations will be treated as zero in summary statistics.

Descriptive statistics of all PK parameters will include arithmetic and geometric mean, median, SD, coefficient of variation (CV), geometric CV, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation.

Summary statistics will be presented for magrolimab serum concentrations at each scheduled time point. Descriptive graphical plots of individual serum concentration-versus-time profiles and mean concentration-versus-time profiles will be generated.

Missing concentration values will be reported as is in data listings. Concentration values below the lower limit of quantitation will be handled as zero in summary statistics, and reported as is in data listings. Any missing PK parameter data will not be imputed.

11.3.2.2. Immunogenicity Analyses

Development of ADAs will be analyzed using a validated immunoassay, using a tiered testing approach – screening, confirmatory, and titer.

Relationship between ADA formation on PK, PD, and safety/efficacy may also be explored, if relevant. Immunogenicity analysis may be performed for rituximab.

11.3.3. Safety Analyses

The statistical analysis of safety data will be conducted for patients in the SAF and will include patients with non-missing data for the particular safety endpoint being analyzed. Safety variables may include, but are not limited to: DLTs, treatment-emergent adverse events (TEAE; AEs satisfy one or both of the following: 1) Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug or the initiation of the subsequent line of anticancer therapy, whichever is earlier. 2) Any AEs leading to discontinuation of study drug.), TRAEs (TEAEs that are considered to be related to any study drugs), vital signs, physical examinations, laboratory tests, ECGs, RO, and ADA assessments.
Data will be presented by Phase 1b antibody combination (magrolimab + rituximab) by dose cohort, Phase 1b chemotherapy combination (magrolimab + R-GemOx) by dose cohort, and Phase 2 antibody combination (magrolimab + rituximab) by arm. Some safety data may be summarized over all Phase 1b dose cohorts and across both Phase 1b and Phase 2 parts. Data may be graphed, summarized, or listed, depending on the amount of data to be reported. Where relevant, safety data will also be presented by the study day/study day interval corresponding to dose administrations within each dose cohort.

11.3.3.1. Adverse Events

The AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or later and the NCI CTCAE v 4.03 (Appendix B) will be used to grade severity of AEs and laboratory toxicities. Patient incidence of TEAEs will be summarized by system organ class and preferred term. TEAEs will also be summarized using Investigator assessment of the relationship to study drug (related or not related). SAEs, including deaths, will be summarized and/or listed for each

dose cohort and for all dose cohorts combined. These events will also be summarized by Phase 2 antibody combination (magrolimab + rituximab) arm (indolent lymphoma and DLBCL) and across all Phase 2 patients. TEAEs resulting in withdrawal from study drug or further study participation will be tabulated and/or listed. DLTs will also be listed.

The AEs that occurred during screening, but before exposure to study drug, will be reported in the AE line listings and appropriately identified as non-TEAEs.

The AEs and SAEs occurring during screening will be reported separately for patients who were screened, but not entered into the study with line listings and/or summary tables, along with relevant demographic data collected.

11.3.3.2. Analysis of Other Safety Endpoints

For select laboratory parameters, changes of laboratory values over time, grade shifts in laboratory value from baseline to worst on-study value and Grade 3 or higher laboratory toxicities will be summarized. The number and incidence of patients developing RO and ADA at any time will be summarized. ECGs, vital signs, and physical examination will be summarized at select time points. Details will be provided in the SAP.

11.4. Clinical Trial Steering Committee Meetings

11.4.1. Clinical Trial Steering Committee Meetings in Phase 2 for Antibody Combination (Magrolimab + Rituximab)

Serial analyses will be conducted in the Phase 2 antibody combination (magrolimab + rituximab) cohort for CTSC meetings to facilitate the decision making on go/no-go based on the safety and efficacy evaluation.

After 14 patients are enrolled at any RP2DS in the Phase 2 antibody combination (magrolimab + rituximab) DLBCL and/or 14 patients in the indolent lymphoma arm have completed a 4-week safety assessment, a safety analysis will be performed. If 33% of patients experience any Grade 3 or greater AE that is assessed as related to study drug (magrolimab and/or rituximab) and results in permanent

discontinuation, withdrawal, or death, then that Phase 2 arm will be stopped. The trial may also be stopped at any time if the CTSC deems that there is an unacceptable safety risk to patients with the study treatment. The trial may otherwise proceed to accrue the second stage if the response criteria described above are met.

If results from the safety analysis described above are deemed safe for continuing the treatment with this regimen in either the DLBCL and/or indolent lymphoma arm and if ≥ 3 out of 14 patients have an objective response in either the DLBCL and/or indolent lymphoma arm, then further enrollment will continue in that arm. Otherwise enrollment in that arm will stop. The CTSC may approve further enrollment and exploration of an additional Phase 2 dose or to explore alternative dose regimens that may enhance efficacy.

In the DLBCL cohort (Phase 2 Cohorts 1 to 3), if the CTSC approves further enrollment after assessment of 14 patients in Phase 2, an analysis for efficacy will be performed after 40 patients in the Phase 2 antibody combination (magrolimab + rituximab) DLBCL cohort. The CTSC will convene and provide recommendations to the Sponsor to proceed with full accrual of the DLBCL cohort, or terminate the study according to the pre-specified stopping rules. For the Phase 2 antibody combination (magrolimab + rituximab) DLBCL cohort, additional enrollment will proceed if the ORR is $\geq 20\%$. For the revised DLBCL cohort (DLBCL Phase 2 Cohort 4), an interim evaluation will be conducted after 20 efficacy-evaluable patients and if the ORR is $\geq 20\%$ (4/20 patients), then enrollment may proceed to 100 patients total.

In the indolent lymphoma cohort, if the CTSC approves further enrollment after assessment of 14 patients in Phase 2, an analysis for efficacy will be performed after at least 24 patients in the Phase 2 antibody combination (magrolimab + rituximab) indolent lymphoma cohort. The CTSC will convene and provide recommendations to the Sponsor to proceed with full accrual of the indolent lymphoma cohort or terminate the study according to the pre-specified stopping

rules. For the Phase 2 antibody combination (magrolimab + rituximab) indolent lymphoma cohort, additional enrollment will proceed if the ORR ≥ 30% or if the CR rate is ≥ 20%.

The response rates needed for further enrollment for both DLBCL and indolent lymphoma cohorts are based on a futility analysis in which response rates lower than specified would halt further enrollment.

11.4.2. Clinical Trial Steering Committee Meetings in Phase 1b for Chemotherapy Combination (Magrolimab + R-GemOx)

The chemotherapy combination (magrolimab + R-GemOx) safety dose-escalation phase will enroll 3 to 6 DLT-evaluable patients at each dose cohort in accordance with a modified 3+3 design. CTSC meetings will decide whether to escalate, de-escalate dose or expand another 10 patients at any dose level. Once a RP2DS is determined by CTSC meeting, 20 patients will be enrolled at this dose level in the chemotherapy combination (magrolimab + R-GemOx) dose-expansion cohort. CTSC meeting may stop ASCT ineligible DLBCL arm for safety reasons relating to study drug (magrolimab and/or R-GemOx).

The CTSC may approve further enrollment and exploration of an additional dose or dosing schedule or to explore alternative dose regimens that may enhance efficacy.

11.4.3. Treatment-Related Toxicity Monitoring

The treatment-related toxicity monitoring is added after completion of study enrollment. It will be monitored at a preset frequency with the stopping boundary listed in Table 11-2 based on actual number of patients at the dose level for each Phase 2 cohort. The boundary will be reviewed retrospectively for all phase 2 cohorts first, then the frequency of review will be every 6 months after patients are treated at least 6 months. This is a Pocock-type boundary (Ivanova 2005) that yields the probability of crossing the boundary of at most 80% when the rate of Grade 4 or higher treatment-related TEAEs is 33%, or the

rate of treatment-related deaths is 15%.

Table 11-2 Stopping Boundary Due to Toxicity for Each Phase 2 Cohort

	Phase 2 Cohort 1	Phase 2 Cohort 2	Phase 2 Cohort 3	Phase 2 Cohort 4
Number of Subjects	**N = 43**	**N = 14**	**N = 31**	**N = 28**
Subjects with Grade 4/5 Treatment-related TEAEs	≥ 16	≥ 5	≥ 11	≥ 10
Subjects with Treatment-related deaths	≥ 7	≥ 2	≥ 5	≥ 5

TEAE = treatment-emergent adverse event

11.5. Clinical Trial Steering Committee

The CTSC will oversee the conduct of the clinical trial. A representative from the Sponsor, usually the Study Medical Monitor or designee, will chair the CTSC. The CTSC will have representation from each participating site in the study. The CTSC will review safety and efficacy data generated during the trial and make decisions about patient recruitment, trial management, initiation of protocol-specific amendments, expansion of cohorts, using higher or lower dose levels or different dosing schedules, defining any new dose cohorts, and identification of the recommended dose and schedule for Phase 2 trials. The composition, structure, and function of the CTSC are defined in the CTSC Charter.

12. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

12.1. Compliance Statement

This study will be conducted in accordance with the protocol and with US FDA and the ICH Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and any applicable local health authority and IRB/IEC requirements.

To the extent applicable, all references to the FDA, Federal Food, Drug, and Cosmetic Act, Code of Federal Regulations (CFR), ICH, GCP, and the like shall be interpreted as also referring to any corresponding requirements of local regulatory

agencies, regulations, and laws. If there is any discrepancy between FDA, ICH, and local requirements, the most stringent standard shall apply.

12.2. Investigator Responsibilities

As required by FDA regulation (21 CFR Part 56) and ICH guidelines for GCP, the Investigator at each study site must obtain IRB/IEC review and approval of the study protocol, ICFs, patient recruitment materials, and any other pertinent documents before any study-related activities involving patients are performed.

As required in 21 CFR Part 50 and ICH guidelines for GCP, the Investigator or designee must comply with the informed consent process, and ensure that each patient enrolled in this clinical study understands the information presented in the IRB/IEC approved ICF and agrees voluntarily to participate in the clinical study.

The Investigator or designee must submit to the IRB/IEC any written safety report or update (e.g., amended IB or safety amendments and updates) provided by the Sponsor or representative, according to the IEC specific reporting requirements.

The Investigator must inform the IRB/IEC of the progress of the clinical study and report any non-administrative changes made to the protocol; in any case, the Investigator must provide an update to the IRB/IEC at least once a year or in accordance with IRB/IEC continuing approval requirements.

The Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Gilead Sciences. Delegation of Authority Form.

The clinical study report must be signed by the Investigator or, in the case of multi-center studies, the Coordinating Investigator. The Coordinating Investigator, identified by Gilead Sciences, will be any or all of the following:

- A recognized expert in the therapeutic area.
- An Investigator who provided significant contributions to either the design

or interpretation of the study.

- An Investigator contributing a high number of eligible patients.

12.3. Institutional Review Board or Independent Ethics Committee

A copy of the protocol, proposed ICF, other written patient information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and ICF must be received by Gilead Sciences before recruitment of patients into the study and shipment of magrolimab.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The Investigator is to notify the IRB/IEC of deviations from the protocol or SAEs occurring at the site and other AE reports received from Gilead Sciences, in accordance with local procedures.

The Investigator is responsible for obtaining annual IRB/IEC approval/renewal as applicable throughout the duration of the study. Copies of the Investigator's reports and the IRB/IEC continuance of approval must be sent to Gilead Sciences.

12.4. Informed Consent and Human Subject Protection

An initial sample ICF is provided for the Investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from Gilead Sciences Study Monitor to the Investigator. The written informed consent document is to be prepared in the language(s) of the potential patient population.

Before a patient's participation in the clinical study, the Investigator is responsible for obtaining written informed consent from the patient or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable

law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

The Investigator is also responsible for asking the patient if the patient has a primary care physician and if the patient agrees to have his/her primary care physician informed of the patient's participation in the clinical study. If the patient agrees to such notification, the Investigator is to inform the patient's primary care physician of the patient's participation in the clinical study. If the patient does not have a primary care physician and the Investigator will be acting in that capacity, the Investigator is to document such in the patient's medical record. The acquisition of informed consent and the patient's agreement or refusal of his/her notification of the primary care physician is to be documented in the patient's medical records, and the ICF is to be signed and personally dated by the patient, or a legally acceptable representative, and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the patient or legally acceptable representative.

If a potential patient is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the ICF to the patient and must allow for questions. Thereafter, both the patient and the witness must sign the ICF to attest that informed consent was freely given and understood.

12.5. Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained for documents submitted to Gilead Sciences, including the following.

- Patients are to be identified by a unique patient identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique patient identification number, include the age at time of enrollment

- For SAEs reported to Gilead Sciences, patients are to be identified by their unique patient identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Gilead Sciences (e.g., signed ICFs) are to be kept in confidence by the Investigator, except as described below.

In compliance with the CFR/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit such individuals to have access to his/her study-related records, including personal information.

12.6. Urgent Safety Measures

The Sponsor or Investigator may take appropriate urgent safety measures to protect trial participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorization. The trial may continue with the urgent safety measures in place. **The Investigator must inform Gilead Sciences IMMEDIATELY if the study site initiates an urgent safety measure**.

The notification must include:

- Date of the urgent safety measure;
- Who made the decision; and
- Why the action was taken.

The Investigator will provide any other information that may be required to enable Gilead Sciences to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and closeout.

12.7. Serious Breaches and Fraud

Within the UK, the Medicines for Human Use (Clinical Trials) Regulations require the Sponsor to notify any "serious breaches" to the Medicines and Healthcare products Regulatory Agency (UK) (MHRA) within 7 days of the Sponsor becoming aware of the breach. A serious breach is defined as “A breach of GCP or the trial protocol which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the patients of the trial; or
- the scientific value of the trial”

Investigators must notify Gilead Sciences immediately if any serious breach of GCP is suspected.

If there is any proof of fraud this must also be reported to Gilead Sciences. All instances of confirmed clinical trial fraud occurring at sites in the UK will be treated according to the procedure for dealing with a serious breach and must be reported to the MHRA within 7 days of the Sponsor becoming aware.

12.8. Study Monitoring

The Gilead Sciences representative(s) are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Gilead Sciences representative(s) are responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Gilead Sciences representative(s) are to have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the Gilead Sciences representative(s) to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

12.9. Audits and Inspections

As stipulated by 21 CFR §312.58 and ICH guidelines for GCP, a representative of the Sponsor, the FDA, or other regulatory agencies may conduct periodic site audits or inspections. The Investigator or designee will provide these representatives with access to all requested materials, including CRFs and supporting source documents. In addition, the Investigator or other qualified study site personnel are to be available to answer questions, hold interviews, and provide facility tours if requested.

12.10. Data Collection and Handling

The Investigator is responsible for complying with the requirements for all assessments and data collection (including patients not receiving protocol-required therapies), as stipulated in the protocol for each patient in the study. For patients who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the SOA (as described in Section 7.1), the Investigator may search publicly available records (where permitted) to ascertain survival status.

This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

The Investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. Data collection will involve the use of the EDC system, to which only authorized personnel will have access. The Investigator agrees to maintain accurate eCRFs (or paper CRFs) and source documentation as part of the case histories. Gilead Sciences will supply the eCRF, which will be completed in English.

The Investigator or designee must enter all results collected during the clinical study into eCRFs (or CRFs). Guidelines for completion of eCRFs will be reviewed with study site personnel at the site initiation visits. Investigators are responsible for approval of the entered/corrected data.

All entries made on the eCRF (or CRF), must be verifiable against source documents. In addition to periodic monitoring occurring within the system by study monitors, programmatic edit checks and data listings will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks, queries may be electronically issued to the clinical study sites and electronically resolved by those sites.

All data collected in the context of this study will be stored and evaluated according to regulatory requirements and applicable guidance for electronic records.

Also, data will be stored and evaluated in such a way as to assure patient confidentiality in accordance with the legal and regulatory requirements applying to protected health information. Study records (e.g., copies of eCRFs, regulatory documents) will be retained at the study site, along with adequate source documentation. The study file and all source data must be retained for the time period required by applicable regulatory requirements and will not be destroyed until written notification is given by the Sponsor or designee for destruction.

12.11. Maintenance of Source Documents and Record Retention

As stipulated by 21 CFR §312.57 and ICH E6 GCP Consolidated Guidance Section 8, the Investigator or designee will maintain source documentation for this clinical study that documents the treatment and study course of patients as described in the study manual.

Source documents are original documents, data, and records from which the patient’s CRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries,

microfiches, radiographs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Gilead Sciences and/or applicable regulatory authorities.

The Investigator must retain all essential documents for this clinical study until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of magrolimab. However, the Investigator may need to retain these documents for a longer period, if required by the applicable regulatory requirements or by an agreement with the Sponsor. A Sponsor representative will be responsible for informing the Investigator and study site regarding when they no longer need to retain these documents. Before destroying any records, the Investigator must notify the Sponsor and reach agreement on record destruction, or the Sponsor may request an additional retention period.

12.12. Long-term Retention of Samples for Additional Future Research

Blood, tumor, or bone marrow specimens will be cryopreserved for additional analyses. These samples will be retained for long-term storage by the Sponsor and described in the informed consent.

Any blood, tissue, or biomarker sample collected according to the SOA (Section 7.1) may be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study patients. This includes testing to ensure that analytical methods produce reliable and valid data throughout the course of the study. It may also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the

site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure data integrity and control.

If permitted by local law and if informed consent is provided by the patient, Gilead Sciences may do additional testing on remaining samples (i.e., residual and back-up) to investigate and better understand NHL and the dose response and/or prediction of response to magrolimab; to characterize antibody response; and to characterize aspects of the molecule (e.g., MOA/target, metabolites). Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples may be retained for up to 20 years.

CCI [redacted]

The patient retains the right to request that the sample material be destroyed by contacting the Investigator. Following the request from the patient, the Investigator is to provide the Sponsor with the required study and patient number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures have been completed.

Information collected from samples prior to the request for destruction will be retained by the Sponsor. The Sponsor is the exclusive owner of any data, discoveries, and derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the patient through the Investigator, at the end of the storage period or as appropriate (e.g., the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this

research project, the Sponsor owns the commercial product. The patient has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

12.13. Financing and Insurance

The Sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

13. REFERENCES

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Boasman K, Bridle C, Simmonds M, et al. Role of pro-phagocytic calreticulin and anti-phagocytic CD47 in MDS and MPN models treated with azacitidine or ruxolitinib. EHA 2017 abstract only. https://learningcenter.ehaweb.org/eha/2017/22nd/182624/kristian.boasman.role.of.pr o-phagocytic.calreticulin.and.anti-phagocytic.cd47.html.

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14. APPENDICES

APPENDIX A. RITUXAN®/MABTHERA (RITUXIMAB) PRESCRIBING INFORMATION

RITUXAN®(rituximab) prescribing information

Available online: http://www.gene.com/download/pdf/rituxan_prescribing.pdf

Accessed 27 April 2017

MabThera®(rituximab) prescribing information

Available online:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf

Accessed 27 April 2017

APPENDIX B NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI), Version 4.03

Publication date: 28 May 2009 (v4.03: 14 June 2010)

https://evs.nci.nih.gov/ftp1/CTCAE/About.html

Accessed 27 April 2017

APPENDIX C THE LUGANO CLASSIFICATION AND LYRIC CRITERIA FOR LYMPHOMAS

Publications:

LUGANO CLASSIFICATION:

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-3068.

LYRIC CRITERIA:

Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood. 2016 Sep 20;128(21):2489-2496.

Available online:
http://www.bloodjournal.org/content/bloodjournal/128/21/2489.full.pdf

Accessed 25 April 2017

APPENDIX D ECOG PERFORMANCE STATUS

Eastern Cooperative Oncology Group Scale of Performance Status

Publication:

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

Karnofsky Performance Status

Publication:

Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.

Available online:

http://ecog-acrin.org/resources/ecog-performance-status

Accessed 7 June 2016

APPENDIX E PERIPHERAL SMEAR ASSESSMENT

Peripheral smears will be assessed by the designated hematopathology service using the following guidelines:

RBC Agglutination	
0–9%	Not reported/absent
10–19%	1+
20–50%	2+
51–75%	3+
> 75%	4+
Spherocytes	
0–1 cells/100 RBCs	Not reported/absent
2–5 cells/100 RBCs	1+
> 5–10 cells/100 RBCs	2+
> 10–30 cells/100 RBCs	3+
> 30 cells/100 RBCs	4+
RBC Fragments/Schistocytes	
0 cells/100 RBCs	Not reported/absent
1–2 cells/100 RBCs	1+
> 2–5 cells/100 RBCs	2+
> 5–10 cells/100 RBCs	3+
> 10 cells/100 RBCs	4+

Abbreviations: RBCs = red blood cells.

All other observed findings: report according to local laboratory hematopathology standard procedures.

If sites are not able to quantify the degree of peripheral smear findings noted above, then the presence or absence of RBC agglutination, spherocytes, and/or RBC fragments/schistocytes must be reported at a minimum.

APPENDIX F GEMZAR® (GEMCITABINE) PRESCRIBING INFORMATION

GEMZAR®(gemcitabine) prescribing information

Available online: https://pi.lilly.com/us/gemzar.pdf

Accessed 18 August 2018

APPENDIX G ELOXATIN® (OXALIPLATIN) PRESCRIBING INFORMATION

ELOXATIN®(oxaliplatin) prescribing information

Available online:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021759s012lbl.pdf

Accessed 18 August 2018

APPENDIX H HISTORY OF PATIENT ENROLLMENT AND ASSESSMENTS

Table H- 1 Antibody Combination (Magrolimab + Rituximab): Phase 1b Schedule of Assessments

Examination		Antibody Combination (Magrolimab + Rituximab): Phase 1b Schedule of Assessments																									
Cycle (28-day Cycles)		1							2 [s]						3 [s]				4 [s]				5+ [s]			
Cycle Day	SC	1	2	8	9	11	15	22	1	2	4	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22
Visit Window (Days)	-30	None		±1					±2			±1			±2											
Assessments																										
Informed consent	X																									
Demographics	X																									
Medical and cancer history	X																									
Inclusion/exclusion criteria	X																									
Enrollment cohort assignment [a]	X																									
Pregnancy test [b]	X	X[c]							X						X				X				X			
CBC with differential, platelets, reticulocytes [b]	X	X	X	X			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X		X	
Peripheral blood smear [d]	X	X[b]	X	X			X	X	X						X											
Serum or plasma chemistry [b]	X	X	X	X			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X		X	
Serum uric acid, phosphorous [b]	X	X	X	X			X																			
Haptoglobin, D-dimer, thrombin time, and plasma fibrinogen [b]	X	X	X	X			X	X							X				X				X			
PT/INR, aPTT [b]	X			X					X						X				X				X			

Examination		Antibody Combination (Magrolimab + Rituximab): Phase 1b Schedule of Assessments																									
Cycle (28-day Cycles)		1							2 [s]						3 [s]				4 [s]				5+ [s]				
Cycle Day	SC	1	2	8	9	11	15	22	1	2	4	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22	
Visit Window (Days)	-30	None		±1					±2		±1				±2												
Assessments																											
Type and screen (ABO/Rh), DAT	X																										
Lymphocyte subset analysis		X							X						X				X				X				
Urinalysis [b]	X						X																				
Correlative studies [e]		X					X		X						X[r]												
Pharmacokinetics [f]		X		X	X	X	X	X	X	X	X	X	X	X	X				X				X [p]				
Antidrug antibodies		X							X						X				X				X				
CD47 receptor occupancy [g]		X	X	X		X	X	X	X			X			X								X [p]				
ECOG performance status	X	X		X			X	X	X						X				X				X				
Vital signs [h]	X	X	X	X		X[n]	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination [i]	X	X[b]		X			X		X				X		X		X		X				X				
DLT assessment [j]									X																		
ECG [k]	X	X		X					X																		
Tumor/lymph node biopsy, CCI (within the screening period and ± 1 week for later samples) [u]	X											X															

Examination		Antibody Combination (Magrolimab + Rituximab): Phase 1b Schedule of Assessments																							
Cycle (28-day Cycles)		1							2 [s]						3 [s]				4 [s]				5+ [s]			
Cycle Day	SC	1	2	8	9	11	15	22	1	2	4	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22
Visit Window (Days)	-30	None		±1					±2			±1			±2											
Assessments																										
Diagnostic imaging [l]	X														X								Q8W[q]			
Bone marrow biopsy[m]	X														X											
Response assessment															X								Q8W [q]			
Adverse events	———																									►
Concomitant medications																										
Study Drug Administration																										
Rituximab [n]				X			X	X	X						X				X				X[n]			
Magrolimab [t]		X		X			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Magrolimab (Loading Dose Cohort only)		X		X[o]		X[o]	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ABO = any of the four blood groups A, B, AB, and O; aPTT = activated partial thromboplastin time; CBC = complete blood count; CR = complete response; DAT = direct antiglobulin test; DLT = dose- limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PT/INR = prothrombin time/international normalized ratio; PE = physical exam; PK = pharmacokinetics; Q8W = every 8 weeks; Rh = Rhesus factor; SC = Screening.

NOTE: Patients who will be transitioned from Phase 1b to Phase 2 dosing may have rituximab extended dosing that occurs on odd cycles rather than even (i.e., dosing on odd cycles will not be considered a protocol deviation); refer to Section 6.2.1.2.

a. First dose of magrolimab must be given within 30 days of signing informed consent.

b. Pre-infusion assessments tests may be collected up to 72 hours before study drug administration during the initial dose; however, with subsequent doses pre-infusion assessments maybe collected up to 24 hours before study drug administration.

c. May use screening pregnancy test performed within 72 hours of first dose.

d. Peripheral blood smear slides will be read at the site, and sent to the Sponsor for storage. Details are provided in Section 7.3.7 and in the Laboratory Manual.
e. Time point details for correlative studies are provided in Table 7-4.
f. Time point details for PK studies are provided in Table 7-5.
g. Time point details for receptor occupancy studies are provided in Table H-4. Receptor occupancy assessment is only required in Phase 1b. Receptor occupancy sample collection in peripheral blood was discontinued in Protocol Amendment 6.
h. Prior to infusion and within 1 hour after the end of each infusion. Details are provided in Section 7.3.2.
i. Full PE at screening, symptom-directed PE thereafter.
j. DLT will be assessed through the first 4 weeks of the study.
k. Single at screening. For Phase 1b only, triplicate within 2 hours prior to rituximab infusion and within 30 minutes of the end of magrolimab infusion (Section 7.3.3).
l. (± 1 week) Refer to Section 7.3.5 for details.
m. Bone marrow biopsy will be performed for response assessment in patients with known bone marrow disease involvement and to confirm CR at any response assessment, where clinically appropriate, and at disease progression.
n. Rituximab will be continued at even cycles in Cycles 6 and beyond until loss of clinical benefit or unacceptable toxicity.
o. Loading Dose Cohort only: Loading doses of magrolimab administered on Days 8 and 11 may be shifted ± 1 day, provided that loading doses are not administered on consecutive days.
p. Starting with Cycle 5, samples to be collected every other cycle (e.g., Cycle 5, 7, and so on).
q. Response assessments may be adjusted by ± 4 weeks to coordinate with treatment cycle timing. After Cycle 3, window is ± 14 days.
r. To be performed with diagnostic imaging (± 7 days from Cycle 3, Day 1).
s. For a Q2W dosing schedule, visits on Days 8 and 22 are not required.
t. For some dose levels, a Day 11 magrolimab loading dose is administered, as well as magrolimab being administered on Days 1 and 15 starting in Cycle 3 (for Dose Level 4). See Table 6-1 for magrolimab dosing schedules according to dose level.
u. Archival tumor tissue may be collected by the Sponsor for correlative studies. The tissue block is preferred, but if not available at least 10 unstained slides are suggested.

Table H- 2 Antibody Combination (Magrolimab + Rituximab): Alternate RP2DS Schedule of Assessments

Examination		Antibody Combination (Magrolimab + Rituximab): Alternate RP2DS Schedule of Assessments																							
Cycle (28-day Cycles)		1							2 q				3 q				4 q				5+ q			
Cycle Day	SC	1	2	8		11	15	22	1	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22
Visit Window (Days)	-30	None		±1					±2	±1			± 2											
Assessments																								
Informed consent	X																							
Demographics	X																							
Medical and cancer history	X																							
Inclusion/exclusion criteria	X																							
Enrollment cohort assignment [a]	X																							
Pregnancy test [b]	X	X[c]							X				X				X				X			
CBC with differential, platelets, reticulocytes [b]	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Peripheral blood smear [d]	X	X [b]	X	X			X	X	X				X											
Serum chemistry [b]	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Serum uric acid, phosphorous [b]	X	X	X	X			X																	
Haptoglobin, D-dimer, thrombin time and plasma fibrinogen [b]	X	X	X	X			X	X					X				X				X			
PT/INR, aPTT [b]	X			X					X				X				X				X			
Type and screen (ABO/Rh), DAT	X																							
Lymphocyte subset analysis		X							X								X				X			
Urinalysis [b]	X						X																	
Correlative studies [e]		X							X				X[o]				X							

Examination		Antibody Combination (Magrolimab + Rituximab): Alternate RP2DS Schedule of Assessments																							
Cycle (28-day Cycles)		1							2 q				3 q				4 q				5+ q			
Cycle Day	SC	1	2	8		11	15	22	1	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22
Visit Window (Days)	-30	None		±1					±2	±1			± 2											
Assessments																								
Pharmacokinetics [f]		X		X			X		X		X		X				X				X[m]			
Antidrug antibodies		X							X				X				X				X[m]			
ECOG performance status	X	X		X			X	X	X				X				X				X			
Vital signs [g]	X	X	X	X		X [p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [h]	X	X[c]		X			X	X	X		X		X		X		X				X			
ECG [i]	X																							
Tumor/lymph node biopsy [j]	X									X[o]														
Diagnostic imaging[k]	X												X								Q2C[n]			
Bone marrow biopsy [l]	X												X											
Response assessment													X								Q2C[n]			►
Adverse events																								►
Concomitant medications																								
Study Drug Administration																								
Rituximab				X			X	X	X				X				X				C5+C6,then Q2C			
Magrolimab		X		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Magrolimab (Loading Dose Cohort only)		X		X[p]		X[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ABO = any of the four blood groups A, B, AB, and O; aPTT = activated partial thromboplastin time; C = cycle number; CBC = complete blood count; CR = complete response; DAT = direct antiglobulin test; DLT = dose-limiting toxicity; ECG = electrocardiogram;

ECOG = Eastern Cooperative Oncology Group; PT/INR = prothrombin time/international normalized ratio; PE = physical exam; PK = pharmacokinetics; Q2C = every 2 cycles; Rh = Rhesus factor; RP2DS = recommended Phase 2 dose and schedule; SC = screening.

a. First dose of magrolimab must be given within 30 days of signing informed consent.
b. Pre-infusion assessments tests may be collected up to 72 hours before study drug administration during the initial dose, however with subsequent doses pre-infusion assessments may be collected up to 24 hours before study drug administration.
c. May use screening pregnancy test performed within 72 hours of first dose.
d. Peripheral blood smear slides will be retained and sent to the Sponsor for storage. Details are provided in Section 7.3.7.
e. Time point details for correlative studies are provided in Table 7-4.
f. Time point details for PK time points are provided in Table 7-3.
g. Prior to infusion and within 30 minutes after the end of each infusion. Details are provided in Section 7.3.2.
h. Full PE at screening, symptom-directed PE thereafter.
i. Single at screening.
j. The tumor/lymph node biopsy is mandatory within the screening period and the window is ± 2 weeks for later samples. Archival tumor tissue may be collected by the Sponsor for correlative studies. The tissue block is preferred, but if not available at least 10 unstained slides are suggested.
k. (± 1 week) Details are provided in Section 7.3.5.
l. Bone marrow biopsy will be performed for response assessment in those patients with known bone marrow disease involvement and also performed to confirm CR at any response assessment, where clinically appropriate, and at disease progression.
m. Starting with Cycle 5, samples to be collected every other cycle (e.g., Cycle 5, 7, and so on).
n. Response assessments may be adjusted by ± 4 weeks to coordinate with treatment cycle timing.
o. To be performed with diagnostic imaging (± 7 days from Cycle 3, Day 1).
p. Loading Dose Cohort only: Loading doses of magrolimab administered on Days 8 and 11 may be shifted ± 1 day, provided that loading doses are not administered on consecutive days.
q. For a Q2W dosing schedule, visits on days 8 and 22 are not required.

Table H- 3 Pharmacokinetic Assessments: Antibody Combination (Magrolimab + Rituximab) Phase 1b

	Cycle 1						Cycle 2						C3-C6	C7+	EOT
Day	**1**	**8**	**9**	**11**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**1**	**—**
Pre-rituximab infusion (within 12 hours)		X			X	X	X						X[a]		X
Pre-magrolimab infusion (within 12 hours)	X	X[b]				X[b]	X[b]			X[b]	X[b]	X[b]	X[a,b]	X[a]	X
1 hour (± 15 min) after magrolimab infusion	X	X			X	X	X			X			X[a]	X[a]	
24 hours (± 8 hours) after most recent magrolimab infusion (Cycle 1 Day 8 or Cycle 2 Day 1)			X					X							
72 hours (± 12 hours) after most recent magrolimab infusion (Cycle 1 Day 8 or Cycle 2 Day 1)				X[c]					X						
1 hour (± 15 min) after rituximab infusion		X					X						X		

Abbreviations: C = cycle number; EOT = end-of-treatment; min = minute(s); PK = pharmacokinetic(s).

Note: Separate PK samples will be collected for magrolimab and rituximab.

a. Starting with Cycle 5, samples to be collected every other cycle (e.g., Cycle 5, 7, and so on).

b. Sample to be collected before rituximab infusion when applicable.

c. Sample to be collected before magrolimab dose when applicable to loading dose cohort.

Table H- 4 CD47 Receptor Occupancy Sample Time Points: Antibody Combination (Magrolimab + Rituximab) Phase 1b Only

Time Points	Cycle 1						Cycle 2		Cycle 3+	EOT
Day	1	2	8	11	15	22	1	8	1	—
Pre-study drug infusion a	X		X	X[c]	X	X	X	X	X[b]	X
1 hour (± 15 min) after magrolimab infusion	X		X	X[c]	X	X			X[b]	
24 hours (± 8 hours) after magrolimab infusion on Day 1		X								
72 hours (± 12 hours) after magrolimab infusion on Day 8				X[c]						

Abbreviations: EOT = end-of-treatment; min = minute(s).

Note: Receptor occupancy samples will be collected and evaluated for Phase 1b only. Receptor occupancy sample collection was discontinued in Protocol Amendment 6.

a. Sample to be collected before rituximab infusion when applicable.

b. Starting with Cycle 5, samples to be collected every other cycle (e.g., Cycle 5, 7, and so on).

c. 72 hour samples to be collected for non-loading dose cohort only. Predose and 1-hr samples to be collected for patients in the loading dose cohort only.

APPENDIX I LYMPHOMA IMMUNOPHENOTYPING

In addition to tumor biopsy to be sent to the central laboratory where sufficient tumor sample is available, local lymphoma immunophenotyping panel is requested. The collected specimen will be divided into 2 portions (1) 1 portion will be sent for local lymphoma immunophenotyping (lymphoma panel), and the results will be reported in the eCRF; and (2) the second portion to be processed locally or sent to the central laboratory as described in the laboratory manual.

Prot 5F9003 amd-12

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	02-Nov-2023 15:48:44