To: CTEP Protocol and Information Office
From: Michael Khodadoust, M.D., Ph.D.
Date: September 5, 2023
Re: Protocol # 10384: "A Phase 1b/2 Study of Hu5F9-G4 (magrolimab) in Combination with Mogamulizumab in Relapsed/Refractory Treated T-Cell Lymphoma"

SUMMARY OF CHANGES – Protocol

Section	Comments
Face Page	Updated version date to September 5, 2023
TOC	Updated page numbers.
Schema, 2.4.4, 6.1	The phase 1b portion of the study has been completed and the RP2D has been defined as Level 1 (30mg/kg magrolimab). Relevant sections of the protocol have been updated to define the phase 2 dose.
3.1, 6.6	The eligibility has been changed to include patients with large cell transformation in the July 31, 2023 version. This introduces an increased likelihood of patients with aggressive disease being included in the study. **This amendment was not approved by the CTEP PRC**, as patients with LCT may respond differently to the Mogamulizumab backbone and the combination, therefore confounding the analysis of primary endpoint of the trial. We understand there is concern with accrual for this trial. We will be happy to discuss with the investigator other ways the protocol might be modified to improve enrollment. **PI Response:** The eligibility has been updated back to the original language without LCT patients.
11	Clarification of the below footnotes were done. g. EOT scans are not required if last scans were done within 28 days. h. maximum number of cycles is 12 l. added RBC genetyping to list
4.1	**Please delete the language within this section and replace it with the current CTEP protocol template language.** **Investigator and Research Associate Registration with CTEP** Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To

<table>
<tr><th>Section</th><th>Comments</th></tr>
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register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems ~~Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam~~. . Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr/. The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.
• Investigator (IVR): MD, DO, or international equivalent,
• Non Physician Investigator (NPIVR): advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD),
• Associate Plus (AP): clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges,
• Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
• Associate Basic (AB): individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

<table>
<tr><th>Documentation Required</th><th>IVR</th><th>NPIVR</th><th>AP</th><th>A</th><th>AB</th></tr>
<tr><td>FDA Form 1572</td><td>✓</td><td>✓</td><td></td><td></td><td></td></tr>
<tr><td>Financial Disclosure Form</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td></tr>
<tr><td>NCI Biosketch (education, training, employment, license, and certification)</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td></tr>
<tr><td>GCP training</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td></tr>
<tr><td>Agent Shipment Form (if applicable)</td><td>✓</td><td></td><td></td><td></td><td></td></tr>
<tr><td>CV (optional)</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td></tr>
</table>

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

• Addition to a site roster,
• Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN,
• Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval, and
</td></tr>
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Section	Comments
	• Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL). In addition, all investigators acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization. Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov **PI Response:** Done
4.2	**Please revise within this section as shown to reflect the current CTEP protocol template language.** In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria ~~to complete~~ for the site to be able to have an Approved status following processing of the IRB/REB approval record ~~to be completed~~: • ~~Holds~~ Have an active CTEP status; • ~~Active~~ Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster; • If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record; • Include~~s~~ the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; • List~~s~~ all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and • ~~Holds~~ Have the appropriate CTEP registration type for the protocol. **Additional Requirements** Additional site requirements to obtain an approved site registration status include: • An active Federal Wide Assurance (FWA) number; • An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); • An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and

Section	Comments
	Compliance with all applicable protocol-specific requirements (PSRs). **PI Response:** Done

4.2.1	**Please revise within this section as shown to reflect the current CTEP protocol template language.**
	
	Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:
	• Log in to the CTSU members' website (https://www.ctsu.org) ~~using your CTEP-IAM username and password,~~
	• Click on *Protocols* in the upper left of the screen
	  ○ Enter the protocol number in the search field at the top of the protocol tree, or
	  ○ Click on the By Lead Organization folder to expand, then select LAO-CA043 and protocol number 10384.
	
	Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration*, to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)
	
	PI Response: Done

4.2.2	**Please revise within this section as shown to reflect the current CTEP protocol template language.**
	• Specimen Tracking System Training Requirement:
	  ○ All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
	  ○ Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
	  ○ The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. ~~However, new versions of the Specimen Tracking System may require new training.~~ Users are strongly encouraged to take a refresher of the training if they have not entered specimen data for an extended period of time
	  ○ This training will need to be completed before the first patient enrollment at a given site.
	
	Please contact STS Support at Theradex for the training

Section	Comments
	(STS.Support@theradex.com ~~Theradex phone: 609-799-7580~~). **PI Response:** Done
4.2.2	**Please revise within this section as shown to reflect the current CTEP protocol template language.** • Specimen Tracking System Training Requirement: o All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training. o Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal. o The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. ~~However, new versions of the Specimen Tracking System may require new training.~~ Users are strongly encouraged to take a refresher of the training if they have not entered specimen data for an extended period of time o This training will need to be completed before the first patient enrollment at a given site. Please contact STS Support at Theradex for the training (STS.Support@theradex.com ~~Theradex phone: 609-799-7580~~). **PI Response:** Done
4.2.3	**Please revise as shown, to reflect the updated CTEP protocol template language.** Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and to activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and ~~include a Master Task List, which describes~~ describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List. **PI Response:** Done

Section	Comments
4.2.4	**Please revise within this section as shown, to reflect the updated CTEP protocol template language.** Site's registration status may be verified on the CTSU members' website. **PI Response:** Done
4.3.1	**Please revise within this section as shown, to reflect the updated CTEP protocol template language.** Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with ~~the registration system~~ patient enrollment in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study. **PI Response:** Done
13.2	**Please revise as shown, to reflect the updated CTEP protocol template language.** Medidata Rave is ~~a~~ the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. Requirements to access Rave via iMedidata: • ~~A valid account, and~~ • Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems, and • Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Rave role requirements: • Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type; • Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and • ~~To hold~~ Rave Read Only or Rave SLA role ~~site staff~~ must have at a minimum ~~hold~~ an Associate (A) registration type. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required. If the study has a Delegation of Tasks Log (DTL), individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Section	Comments
	Upon initial site registration approval for the study in ~~Regulatory Supposrt System (RSS)~~ the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management > Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study-specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name. Site staff ~~that~~ who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in ~~RSS~~ the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (*Medidata Account Activation and Study Invitation Acceptance*). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section ~~at www.ctsu.org/RAVE~~/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com. **PI Response:** Done
13.3	**Please delete the language within this section and replace it with the current CTEP protocol template language. Instructions to the protocol author appear in blue italics and should not be added to the protocol document.** **Data Quality Portal** The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics. The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a

Section	Comments
	regular basis to manage specified queries and delinquent forms. The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available on the DQP modules. CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website. To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules. *Include the following paragraph only if study is not using the Calendaring functionality in Rave; otherwise, delete.* This study does not use the Rave Calendaring functionality and therefore the DQP Delinquent Forms module will not include details for this study, and the DQP Summary table on the Rave Home page will display *N/A* for the Total Delinquencies summary count. **PI Response:** Done
10.3.1	**Please revise within this section as shown, to reflect the updated CTEP protocol template language.** Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 ~~D~~days after the ~~Last Administration~~ last administration of the ~~Investigational Agent/Intervention~~ investigational study agent/intervention are collected using the Late Adverse Event form. Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave: • The reporting period (course/cycle) is correct; and • AEs are recorded and complete (no missing fields) and the form is query-free.

Section	Comments
	The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation. Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS. **PI Response:** Done
9.2	Please insert an "International Planned Enrollment Report" table for the treatment phase of the study since Princess Margaret Cancer Center is listed as a participant. **PI Response:** This has been inserted.

NCI Protocol #: 10384

Local Protocol #: PhII-203

ClinicalTrials.gov Identifier: NCT04541017

TITLE: A Phase 1b/2 Study of Hu5F9-G4 (magrolimab) in Combination with Mogamulizumab in Relapsed/Refractory Treated T- cell Lymphoma

Corresponding Organization: **LAO-CA043** / City of Hope Comprehensive Cancer Center LAO

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Participating Organizations

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / UPMC Hillman Cancer Center LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO
EDDOP / Early Drug Development Opportunity Program

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NCI-Supplied Agent: Hu5F9-G4 (magrolimab) (NSC 809249)
Other Agent(s): KW-0761 (mogamulizumab) (NSC 791064)

IND #: [redacted]
IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:

Original / May 7, 2020
Revision 1 / July 6, 2020
Revision 2 / August 7, 2020
Revision 3a / September 25, 2020
Revision 3b / October 5, 2020
Revision 4 / October 28, 2020
Revision 5 / December 18, 2020
Revision 6 / November 4, 2021
Revision 7 / January 24, 2022
Revision 8 / July 14, 2022
Revision 9 / August 9, 2022
Revision 10 / May 30, 2023
Revision 11 / July 31, 2023 (disapproved)
Revision 12 / September 5, 2023

SCHEMA

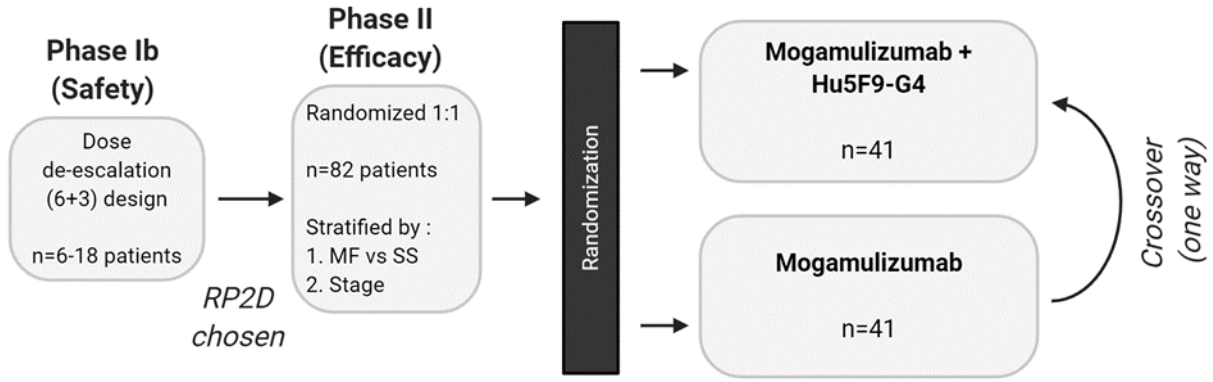

Figure 1: Overall Trial Schema

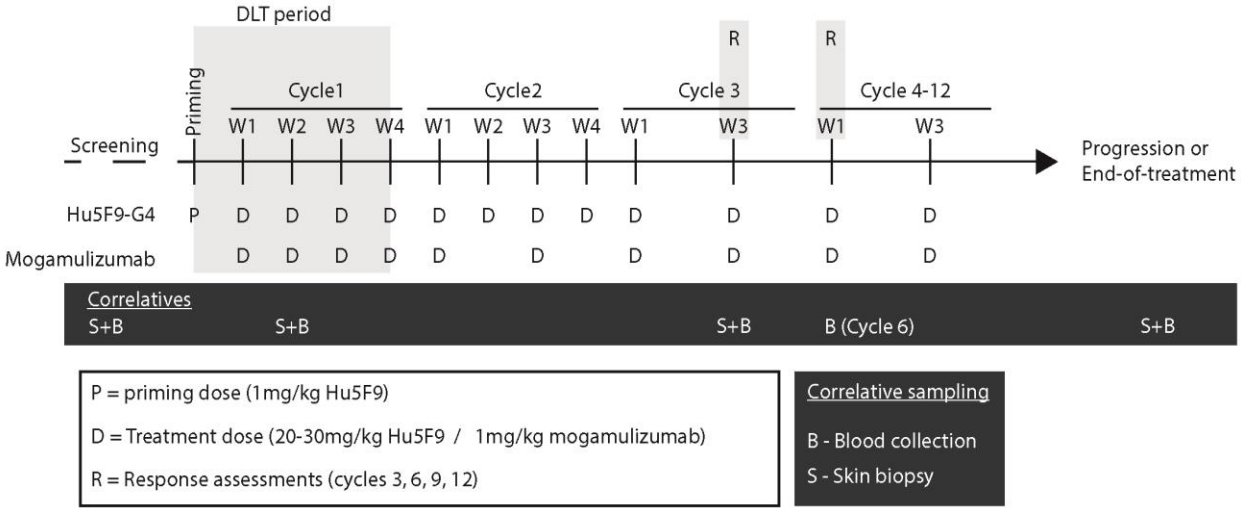

Figure 2: Treatment, Response Assessment, and Correlative Sampling Schedule for Phase 1b and Phase 2
DLT = dose limiting toxicity; q12 = every 12 weeks

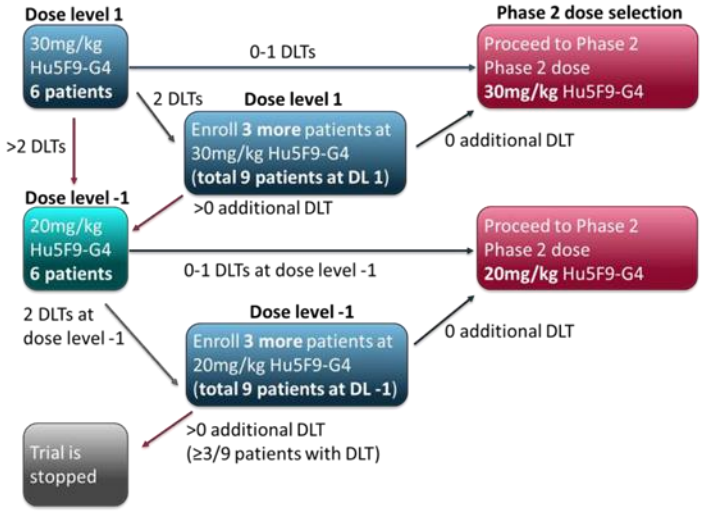

Figure 3: Phase 1b Dose De-escalation Design
DLT = dose limiting toxicity; DL = dose level

Table 1: Dose De-escalation Schedule for Phase 1b

Dose De-escalation Schedule			
Dose Level	**Dose**		**Cycle Length**
	Hu5F9-G4 (Magrolimab)	**Mogamulizumab**	
Level 1 (starting dose level)	1 mg/kg IV priming dose; Then 30 mg/kg IV weekly in Cycles 1 & 2 followed by Q2W in ≥ Cycle 3. Give before mogamulizumab.	1 mg/kg IV (weekly for first cycle then Q2W starting cycle 2)	28 Days
Level -1	1 mg/kg IV priming dose; Then 20 mg/kg IV weekly in Cycles 1 & 2 followed by Q2W in ≥ Cycle 3. Give before mogamulizumab.	1 mg/kg IV (weekly for first cycle then Q2W starting cycle 2)	28 Days
Q2W = Every 2 weeks, IV = Intravenous			

Phase 2 Design:
The phase 1b portion has been completed and the phase 2 portion of the protocol is now open.. There was one DLT identified in the phase 1b portion of the trial with 6 patients treated at dose Level 1. Therefore, the recommended phase 2 dose (RP2D) was established as **Level 1 (30mg/kg magrolimab starting cycle 1).** The phase 2 portion will be a two-arm, randomized, open-label design. This cohort will seek to determine whether Hu5F9-G4 (magrolimab) plus

mogamulizumab will have improved efficacy as compared to mogamulizumab alone. We will enroll 82 patients with relapsed or refractory mycosis fungoides (MF) / Sézary Syndrome (SS). Patients will be randomized 1:1 to either Hu5F9-G4 (magrolimab) plus mogamulizumab or mogamulizumab alone. Randomization will be stratified by 2 characteristics: 1) Disease type (MF *vs* SS) and 2) Stage (1B-2A *vs* 2B-IV). To encourage accrual and to better assess the added effect of Hu5F9-G4 (magrolimab), the trial will allow for one-way crossover from the mogamulizumab only arm to the combination arm. Crossover will be allowed for patients with progressive disease or stable disease lasting 6 months. While not typically a criterion for crossover in other cancers, prolonged stable disease has not been an acceptable outcome for this patient population due to the presence of symptoms associated with ongoing disease.

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 Phase 1

1.1.1.1 To characterize the safety and toxicity profile and to determine a safe recommended phase 2 dose (RP2D) of Hu5F9-G4 (magrolimab) when given in combination with mogamulizumab

1.1.2 Phase 2

1.1.2.1 To compare the proportion of patients who achieve a partial or complete response lasting at least 6 months (ORR6) of the combination of Hu5F9-G4 (magrolimab) and mogamulizumab versus mogamulizumab alone

1.2 Secondary Objectives

1.2.1 Phase 1

1.2.2 To observe and record anti-tumor activity. Although the clinical benefit of these drugs has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

1.2.3 Phase 2

1.2.3.1 To compare the efficacy of the combination of Hu5F9-G4 (magrolimab) and mogamulizumab versus mogamulizumab alone with respect to the following endpoints:

- Overall Response Rate (ORR); Overall Response Rate lasting at least 4 months (ORR4); Overall Response Rate lasting at least 12 months (ORR12)
- Duration of response (DOR)
- Progression-free survival (PFS)
- Time to next treatment (TTNT)

1.3 Exploratory Objectives

1.3.1 Phase 1 and Phase 2

1.3.1.1 To identify potential biomarkers that correlate with response to mogamulizumab and Hu5F9-G4 (magrolimab) including

- Expression of CCR4
- Somatic mutations and germline polymorphisms
- Phenotyping of lymphoma and immune microenvironment
- Functional assay of phagocytosis

2. BACKGROUND

2.1 Study Diseases

2.1.1 Cutaneous T-cell Lymphomas (CTCL)

CTCLs encompass a heterogeneous group of lymphomas that involve the skin but may also involve lymph nodes, blood, and visceral organs. CTCL comprises approximately 25% of all T-cell lymphomas. Mycosis fungoides (MF) is the most common type of CTCL. MF exhibits an epidermotropic clonal expansion of CD4+ T helper cells that induces pleomorphic skin lesions. MF may present gradually over many years as an indolent, chronic skin disease or present with more rapidly advancing skin disease, especially in those with worse prognostic factors such as folliculotropism or large cell transformation. Sézary syndrome (SS) is a leukemic variant of CTCL in which subjects have generalized erythroderma and are at risk for lymph node and visceral disease. There has been a continued increase in overall annual incidence in MF/SS (currently approximately 0.9 per 100,000 persons in the United States) (Horwitz *et al*., 2008). There is a 2:1 male to female prevalence and peak age of presentation is 55 to 60 years. It is rarely seen in the pediatric age group.

The clinical presentation of MF/SS can vary widely among patients. The International Society for Cutaneous Lymphomas/European Organization for Research and Treatment of Cancer (ISCL/EORTC) classification system includes a characterization of both the surface area of involved skin as well as the quality of the skin lesions (patch, plaque, or tumor). Additionally, staging incorporates the burden of disease present in the blood and lymph node compartments, as well as the presence of any visceral sites of disease.

Prognosis of patients with advanced stage (stage IIB and higher) remains poor with a median overall survival of 63 months (Scarisbrick *et al.*, 2015). The most important prognostic factors include overall clinical stage, T-classification, and extracutaneous disease. Other factors associated with poor prognosis include older age, large cell transformation, and folliculotropic disease (Scarisbrick *et al.*, 2015).

Systemic therapies are the mainstay of treatment for patients with more advanced stage disease. These therapies include retinoids, low-dose methotrexate, interferons (alpha and gamma), extracorporeal photopheresis, histone deacetylase (HDAC) inhibitors (vorinostat, romidepsin), brentuximab vedotin, cytotoxic chemotherapeutic agents (pralatrexate, liposomal doxorubicin, gemcitabine), pembrolizumab, and mogamulizumab. Despite the large number of agents available for treatment, response rates to most treatments are 30-35% (Scarisbrick *et al.*, 2015). Complete responses are uncommon, and the duration of response tends to be short-lived, typically 6-12 months. There is a need for new therapies capable of yielding more durable responses.

2.1.2 Chemokine Receptor 4 (CCR4) and T-cell lymphoma

CCR4 is a chemokine receptor for both macrophage-derived chemokine (MDC, CCL22) and thymus- and activation-regulated chemokine (TARC, CCL17). It is expressed by certain T-cell subsets including regulatory T-cells (Tregs), cutaneous lymphocyte antigen-positive skin-homing T cells and some Th2 cells. CCR4 expression on Tregs appears to be selective for Forkhead Box P3 (FOXP3)^{hi}, CD45RA- "effector-type" Tregs that are a potently suppressive class of Tregs (Sugiyama *et al.*, 2013). Therefore, therapies targeting CCR4 are currently being explored as a

form of cancer immunotherapy to deplete Tregs and promote tumor immunity (Sugiyama *et al.*, 2013; Berlato *et al*., 2017; Tanaka and Sakaguchi, 2017).

CCR4 is also frequently expressed by the neoplastic T-cell in several T-cell malignancies. CCR4 expression was detectable in skin biopsies in 100% of 290 patients with MF or SS without large cell transformation (Kim *et al.*, 2018) and was expressed on ≥10% of the infiltrating lymphoid cells in 97% (280/290) of patients. Expression of CCR4 in patients with MF/SS with large cell transformation has ranged from 41-100% in small studies (Jones *et al.*, 2000; Ishida *et al.*, 2004). CCR4 is also frequently expressed in ATLL, with expression detected in 88% (91/103) of patients (Ishida *et al.*, 2004). Other subtypes of peripheral T-Cell lymphoma (PTCL) including anaplastic large cell lymphoma (ALCL), PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and natural killer (NK)/T-cell lymphomas may express CCR4. One study found expression of CCR4 in 28% of PTCL cases when excluding ATLL and CTCL (Ishida *et al.*, 2004). Another phase 2 trial that enrolled CCR4- expressing PTCL and CTCL found 78% of screened patients had CCR4 expression (defined as ≥10% expression by tumor cells) (Ogura *et al*., 2014).

2.2 CTEP IND Agent

2.2.1 Hu5F9-G4 (magrolimab)

Hu5F9-G4 (magrolimab) is a first-in-class anticancer therapeutic agent targeting the cluster of differentiation (CD) 47 signal regulatory protein alpha (SIRPα) axis (Liu, J., *et al.*, 2015; Huang *et al.*, 2017). Hu5F9-G4 (magrolimab) is a recombinant humanized anti-CD47 monoclonal antibody of the IgG4 kappa isotype containing a Ser-Pro (S-P) substitution in the hinge region (position 228) of the heavy chain to reduce fragment antigen-binding (Fab) arm exchange (Liu, J., *et al.*, 2015). Hu5F9-G4 (magrolimab) binds to human CD47 on target malignant cells, blocks the anti-phagocytic signal to macrophages, enhances tumor cell phagocytosis, and elicits an anti-tumor T-cell response (Huang *et al.*, 2017; Liu *et al.*, 2017).

Hu5F9-G4 (magrolimab) blocks the interaction of CD47 with its ligands and enables phagocytosis of human cancer cells (Liu, J., *et al.*, 2015). The activity of Hu5F9-G4 (magrolimab) is primarily dependent on blocking CD47 binding to SIRPα and not on the recruitment of fragment crystallizable (Fc)-dependent effector functions. Most normal cells lack expression of pro-phagocytic signals and are unaffected by Hu5F9-G4 (magrolimab) binding to CD47 (Feng *et al.*, 2015). However, blockade of CD47 in tumors can enhance macrophage phagocytosis of cancer cells, and in preclinical studies, this results in a profound antitumor effect against solid tumors and hematological malignancies (Liu, J., *et al.*, 2015; Chan *et al*., 2009).

CD47 is widely expressed and has been identified as a key molecule mediating cancer cell evasion of phagocytosis by the innate immune system (Liu, J., *et al.*, 2015). It provides an anti-phagocytic signal by binding to the N-terminus of SIRPα on immune cells and suppresses phagocytosis (Huang *et al.*, 2017). Hematopoietic stem cells transiently upregulate CD47 expression to escape phagocytosis by macrophages before and during mobilization (Jaiswal *et al.*, 2009). The pathological role of CD47 is commonly responsible for the escape of malignant cancer cells from immune- surveillance. CD47 expression is increased on the surface of cancer

cells from many diverse human tumor types including head and neck cancer, melanoma, breast, lung, ovarian, pancreatic, colon, bladder, prostate, leiomyosarcoma, glioblastoma, medulloblastoma, glioma, lymphoma, leukemia, and multiple myeloma (Chan *et al*., 2009; Jaiswal *et al.*, 2009; Majeti *et al*., 2009; Chao *et al*., 2010a; Chao *et al.*, 2010b; Chao *et al.*, 2012; Krampitz *et al*., 2016; Edris *et al.*, 2012; Gholamin *et al*., 2017, Weiskopsf *et al*., 2016). CD47 overexpression has been associated with poor prognosis in leukemia, non-Hodgkin lymphoma (NHL), bladder cancer, breast cancer, and other cancers (Huang *et al*., 2017; Majeti *et al*., 2009; Chao *et al.*, 2010a; Chan *et al.*, 2009; Willingham *et al*., 2012). Furthermore, elevated CD47 messenger RNA (mRNA) expression correlates with a worse overall survival for multiple types of cancer (Willingham *et al.*, 2012). In murine xenograft studies, CD47-blocking antibodies can inhibit human cancer growth and metastasis by enabling the phagocytosis of cancer stem cells (CSCs) from various hematological malignancies and solid tumors. CD47-blocking antibodies have been shown to exhibit potent synergy with tumor-specific monoclonal antibodies, such as rituximab, cetuximab, and trastuzumab (Chao *et al.*, 2010a; Weiskopf *et al.*, 2013).

Hu5F9-G4 (magrolimab) has demonstrated antitumor activity in breast, ovarian, brain, and bladder cancers, acute myeloid leukemia (AML), NHL, and other malignancies in preclinical studies (Chan *et al.*, 2009, Gholamin *et al.*, 2017, Liu, J., *et al.*, 2015, Sikic *et al.*, 2019, Willingham *et al.*, 2012).

2.2.1.1 Mechanism of Action

Hu5F9-G4 (magrolimab) is an anti-CD47 monoclonal antibody that disrupts the CD47/SIRPα interaction to induce macrophage-mediated phagocytosis (Liu, J., *et al.*, 2015). Hu5F9-G4 (magrolimab) selectively binds to CD47 on tumor cells and prevents it from binding to SIRPα. This inhibits CD47/SIRP signaling, causing the activation of macrophages which in the presence of additional prophagocytic signals, such as calreticulin can initiate specific tumor cell phagocytosis (Chao *et al.*, 2010b). Inhibiting CD47 signaling can also initiate an anti-tumor T-lymphocyte immune response and T-cell-mediated killing (Liu, X., *et al.*, 2015).

2.2.1.2 Summary of Nonclinical Experience

The therapeutic effect of Hu5F9-G4 (magrolimab) was evaluated in human AML xenograft models *in vivo* with two independent primary patient samples (SU028 and SU048) (Investigator's Brochure, 2019). Therapy was initiated with daily intraperitoneal (IP) injection of either control mouse IgG or 100 mcg of Hu5F9-G4 (magrolimab). The therapeutic response was monitored by analyzing the burden of AML cells in repeated bone marrow aspirates. Daily doses of 100 mcg of Hu5F9-G4 (magrolimab) over 2 weeks cleared AML in the bone marrow of all mice at the end of treatment with recovery of normal hematopoiesis in the bone marrow, leading to a major survival benefit compared to control.

The pharmacokinetics (PK) and toxicokinetics (TK) of Hu5F9-G4 (magrolimab) were studied in single- and repeat-dose (non-Good Laboratory Practice [GLP] and GLP) studies in the cynomolgus monkey and an 8-week pivotal toxicology study (Investigator's Brochure, 2019). Hu5F9-G4 (magrolimab) has nonlinear PK with a varied half-life ($t_{1/2}$), ranging from approximately 5 to 250 hours following single and multiple doses. The volume of distribution

approximated monkey serum volume, as expected for a monoclonal antibody. The $t_{1/2}$ appears to increase and clearance appears to decrease with increasing dose and with repeated dosing, suggesting saturation of target-mediated clearance (CL) through the endogenous CD47 cellular sink.

2.2.1.2 Summary of Clinical Experience

As of July 24, 2019, 401 patients have received Hu5F9-G4 (magrolimab) as monotherapy and in combination in six company sponsored clinical trials (SCI-CD47-001, SCI-CD47-002, 5F9003, 5F9004, 5F9005, and 5F9006) (Investigator's Brochure, 2019). The two monotherapy studies include Study SCI-CD47-001, a phase 1 study in advanced solid tumor and lymphoma patients and Study SCI-CD47-002, a phase 1 study in relapsed/refractory (R/R) AML patients. The four combination studies include Study 5F9003, a phase 1b/2 of Hu5F9-G4 (magrolimab) with rituximab in NHL patients; Study 5F9004, a phase 1b/2 of Hu5F9-G4 (magrolimab) with cetuximab in solid tumor and colorectal cancer (CRC) patients; Study 5F9005, a phase 1b study of Hu5F9-G4 (magrolimab) with azacitidine in AML and myelodysplastic syndrome (MDS) patients; and Study 5F9006, a phase 1b study of Hu5F9-G4 (magrolimab) with avelumab in solid tumor and ovarian cancer patients.

2.2.1.2.1 Clinical Pharmacokinetics (PK)

The PK data are available from 58 patients in the first in human (FIH) study, Study SCI-CD47-001 (Investigator's Brochure, 2019). Hu5F9-G4 (magrolimab) was administered at a dose range of .01 mg/kg to 30 mg/kg. The area under the concentration-time curve (AUC) and maximum plasma concentration (C_{max}) show greater than dose-proportional increases at doses ≤10 mg/kg and dose-proportional changes at 10 to 30 mg/kg. After priming dose of 1 mg/kg, a geometric mean C_{max} of 0.682 mcg/mL (mg/L) was observed. After the second dose of 1 mg/kg, the geometric mean C_{max} was approximately 10-fold higher at 5.83 mcg/mL. On continuous dosing, the geometric mean C_{max} increased by another 2-fold to approximately 10 mcg/mL. The increase after the second dose was consistent with multiple dose accumulation. This suggests time-dependent PK at 1 mg/kg between the first and the second doses. Due to the small number of patients, this phenomenon could not be characterized at other doses. The mean terminal $t_{1/2}$ derived from the PK parameters was approximately 2 weeks at doses ≥10 mg/kg weekly. The PK of Hu5F9-G4 (magrolimab) is similar to other humanized monoclonal antibodies targeted towards cell-surface receptors. After multiple weekly doses ≥10 mg/kg, the CD47 antigen sink is fully saturated.

The rate of anti-drug antibody (ADA) occurrence was low (<10%) and typical for a humanized antibody (Investigator's Brochure, 2019). Comparison of the PK of the ADA-positive and ADA-negative patients indicated that there was no impact of ADA occurrence on PK. There was no clear correlation between ADA occurrence and safety events.

2.2.1.2.2 Clinical Safety Summary

As of July 24, 2019, 401 (324 solid tumor/lymphoma and 77 AML/MDS patients) patients have received at least one dose of Hu5F9-G4 (magrolimab) as monotherapy or in combination

(Investigator's Brochure, 2019). Patients reported anemia (35.9%), fatigue (31.9%), headache (30.7%), infusion-related reaction (IRR) (25.7%), pyrexia (22.9%), chills (21.4%), nausea (19.5%), hemagglutination (14.5%), and vomiting (11.0%) as the most common treatment-related adverse events (AEs).

A total of 397 serious adverse events (SAEs) have been reported in patients across all six clinical studies (Investigator's Brochure, 2019). The most commonly reported SAEs include febrile neutropenia (40 events), IRRs (23 events), malignant neoplasm progression (20 events), small intestinal obstruction (17 events), pneumonia (16 events), anemia (15 events), and pyrexia (14 events). Only three of the febrile neutropenia SAEs were considered related to Hu5F9-G4 (magrolimab) and none were reported in Studies 5F9004 and 5F9006, which enrolled only solid tumor patients. Twenty-one IRRs were considered related to Hu5F9-G4 (magrolimab), one was attributed to cetuximab only, and one was attributed to rituximab only.

Of the 397 SAEs, 86 were considered related to Hu5F9-G4 (magrolimab) (Investigator's Brochure, 2019). The most frequently reported serious adverse reactions (SARs) included IRR (21 events), anemia (11 events), pyrexia (7 events), and thrombocytopenia (4 events). Anemia and IRR have been identified as risks associated with Hu5F9-G4 (magrolimab), and four of the seven pyrexia SARs occurred within the 24 hours following a Hu5F9-G4 (magrolimab) infusion and could, therefore, be considered part of an IRR. No maximum tolerated dose (MTD) has been determined as monotherapy or in combination. No deaths have been attributed to Hu5F9-G4 (magrolimab) administration.

The RP2D for solid tumor and lymphoma patients is 1 mg/kg (priming) followed by 30 mg/kg once every week for the first two cycles (28 days/cycle), followed by a dose of 30 mg/kg every 2 weeks (Investigator's Brochure, 2019). In MDS and AML patients, the RP2D is 1 mg/kg priming on Days 1 and 4 followed by 15 mg/kg on day 8 and 11 and then 30 mg/kg on days 15, and 22. Weekly doses are continued in Cycle 2 and then in Cycle 3 and beyond 30 mg/kg every 2 weeks is administered. All cycles are 28 days long.

If patients have completed at least 1 cycle of dosing but have a treatment delay of greater than 4 weeks, then re-priming with the Cycle 1 doses and schedules should be instituted upon starting retreatment. Treatment interruptions of less than 4 weeks can resume the treatment schedule without re-priming.

2.2.1.2.3 Clinical Efficacy Summary

In the FIH study, Study SCI-CD47-001, 62 solid tumor and lymphoma patients received Hu5F9-G4 (magrolimab) as monotherapy and were evaluable for efficacy (Investigator's Brochure, 2019). Two of these patients had refractory diffuse large B-cell lymphoma (DLBCL) (Sikic *et al.*, 2019). An additional 10 patients were treated in the CTCL cohort. In the dose-escalation cohorts, 13 treated patients had a diagnosis of ovarian or fallopian tube cancers. Two of these patients, both heavily pretreated and who received 20 mg/kg Hu5F9-G4 (magrolimab), had confirmed partial responses (PRs) with 50% and 44% reduction in tumor measurements. These patients were on treatment for 5.2 and 9.2 months before progressing and they had received more than six prior lines of systemic therapy. No objective responses were observed in other patients.

In the dose escalation cohort, two patients with refractory DLBCL were treated with Hu5F9-G4 (magrolimab) monotherapy. No objective responses were observed; however, one patient had a mixed response (significant decrease in size of multiple tumor lesions, with increase size in others).

For the CTCL patients, 10 patients were treated with Hu5F9-G4 (magrolimab) monotherapy at doses of 20 or 30 mg/kg in Study SCI-CD47-001, and response data are available for 8 CTCL patients (Investigator's Brochure, 2019). No objective responses were observed; however, six patients had stable disease (SD), and two patients had disease progression (PD) as their best response.

As of May 2019, Studies SCI-CD47-002 and 5F9005 evaluated efficacy in AML and MDS patients who received Hu5F9-G4 (magrolimab) as monotherapy and in combination with azacytidine (Investigator's Brochure, 2019). Twenty patients (all AML) were treated in Study SCI-CD47-002 study, and 57 patients (10 R/R AML and MDS, 46 treatment-naïve and unfit for standard induction therapy [TN/U] AML, and 1 rollover cohort) were treated in the Study 5F9005. In Study SCI-CD47-002, 58% of evaluable patients had a reduction in bone marrow blasts, but no objective responses were observed. Two of 18 evaluable patients with long-term SD had marked reductions in bone marrow cellularity, with 1 remaining on treatment for greater than 11 months. One of these patients had a decrease in bone marrow blast count >50% and had a significant increase in T-cell infiltrate in the bone marrow; this patient was on therapy for 11.8 months. In the monotherapy portion of Study 5F9005, the ORR was 10% with one AML patient achieving a response of morphologic leukemia-free state. In the combination portion of Study 5F9005, 25 patients were evaluable for efficacy. In AML, 64% of patients achieved an objective response, including 55% with complete response (CR) + PR. Bone marrow blast reduction was observed in all but one patient on the Hu5F9-G4 (magrolimab) plus azacitidine combination. Hu5F9-G4 (magrolimab) in combination with azacytidine induced high ORRs in newly diagnosed AML patients who are ineligible for induction chemotherapy and newly diagnosed MDS patients who are intermediate to very high risk by Revised International Prognostic Scoring System (IPSS-R).

In Study 5F9003, NHL patients received Hu5F9-G4 (magrolimab) in combination with rituximab (Investigator's Brochure, 2019). Efficacy was evaluated in a total of 97 patients, including 59 DLBCL patients, 35 follicular lymphoma (FL) patients, and 3 marginal zone lymphoma (MZL) patients. The overall ORR for all patients who received at least one dose of Hu5F9-G4 (magrolimab) and had at least one post treatment response assessment was 45%, with 19% achieving a best response of CR. In patients with DLBCL, the ORR was 36%, with 15% achieving a CR. In FL and MZL, the ORR was 61%, with 24% achieving CR. Median time to response (TTR) was 1.7 months (range 1.6 to 6.6 months). In Phase 1b of the study, the median DOR was not reached for either DLBCL or FL patients with a median follow-up of 13.8 and 21 months, respectively.

2.3 Other Agent

2.3.1 Mogamulizumab (KW-0761)

Mogamulizumab is a defucosylated, humanized, monoclonal antibody with enhanced antibody dependent cellular cytotoxicity (ADATA COORDINATING CENTER) targeting CCR4. The lack of fucose results in the antibody eliciting more potent ADATA COORDINATING CENTER than conventionally produced antibodies. Mogamulizumab does not induce complement dependent cytotoxicity. In 2018, the FDA approved mogamulizumab for the treatment of patients with relapsed or refractory MF/SS after at least one prior systemic therapy. This approval was based on the pivotal phase 3 MAVORIC trial. This randomized, open-label trial enrolled 370 patients who were randomized to either mogamulizumab or vorinostat (Kim *et al*., 2018). The trial demonstrated a significant improvement in the primary endpoint of PFS with mogamulizumab treatment as compared to vorinostat (median 7.7 months versus 3.1 months). Improvements were also seen in secondary endpoints including ORR (28% versus 5%) and DOR (median 14.1 months versus 9.1 months). Responses to mogamulizumab were most notable in the blood compartment with a response rate of 68% in blood compartment *vs* 42% in the skin compartment and only 17% in the nodal compartment. Importantly, patients with large-cell transformation (LCT) were excluded from this trial, despite evidence that CCR4 is expressed in MF with LCT (Jones *et al.*, 2000).

In addition to CTCL and ATLL, mogamulizumab has demonstrated some efficacy in other subtypes of PTCL. A Japanese multicenter phase 2 study that included relapsed and refractory CCR4-expressing PTCL found an ORR of 34% in PTCL histologies including PTCL-NOS, AITL, and ALK-negative ALCL (Ogura *et al.*, 2014). A similar European phase 2 study showed an ORR of 13% in PTCL histologies. In trials of both CTCL and PTCL, there has not been an association found between the level of expression of CCR4 and responses to mogamulizumab (Kim *et al*., 2018; Ogura *et al.*, 2014). The CCR4 gene is mutated in 29% of ATLL, resulting in a gain of function and increased expression (Kataoka *et al.*, 2015). Patients with a gain-of-function mutation in CCR4 appear to greatly benefit from mogamulizumab treatment with a 5-year overall survival of 73% versus 26% in patients without CCR4 mutations (Sakamoto *et al.*, 2018)

Mogamulizumab is generally well-tolerated. The most common ≥ grade 3 AEs in the 184 patients treated in the MAVORIC trial were rash/drug eruptions, which led to discontinuation in 7% of mogamulizumab-treated patients.

2.4 Rationale

2.4.1 CD47 as a Therapeutic Target for T-cell lymphomas

CD47 is a surface protein expressed by many normal cells but is frequently overexpressed by cancer cells (Chao *et al*., 2011; Chao *et al*., 2010b; Jaiswal *et al*., 2009; Majeti *et al*., 2009). One of the primary ligands for CD47 is SIRPα, which is expressed on the surface of macrophages, among other cell types (Adams *et al*., 1998). Engagement of CD47 by SIRPα produces an inhibitory signal that decreases the phagocytic function of the macrophage (Weiskopf and Weissman , 2015). It is now recognized that anti-phagocytic signaling through the CD47/SIRPα axis is an important mechanism of cancer evasion from phagocytic clearance. Blockade of CD47/SIRPα signaling, for example by antibodies targeting CD47, can promote phagocytosis and elimination of tumor cells (Chao *et al*., 2010a). Murine patient xenograft models have

demonstrated that antibodies blocking CD47 promote phagocytosis of lymphoma cells and inhibit human lymphoma growth (Chao *et al*., 2010a). Sezary cells have high expression of surface CD47 and overexpression associates with a worse prognosis (Johnson *et al*., 2019). When co-incubated with macrophages, blockade of CD47 promoted selective phagocytosis of Sezary cells, but not normal CD4 T-cells (Johnson *et al*., 2019).

TTI-621 is a decoy receptor for CD47 capable of blocking CD47/SIRPα signaling. The molecule is an ADATA COORDINATING CENTER-competent fusion protein composed of the CD47-binding domain of human SIRPα linked to the Fc region of human immunoglobulin G1. A multicenter phase 1 study of TTI-621 in relapsed and refractory MF/SS has yielded promising results (Querfeld *et al*., 2018). This trial treated patients with intralesional injection of TTI-621. Rapid responses were observed even after a single dose. Remarkably, these responses were not limited to the injected lesion, as abscopal responses were common. In all, 15 of 17 patients (88%) had some measurable improvement and 7 of 17 patients (41%) had ≥50% improvement in measured lesions. Thus, it appears blockade of CD47 signaling may be an effective strategy for CTCL.

2.4.2 Rationale for the combination of mogamulizumab and Hu5F9-G4 (magrolimab)

There is strong preclinical and clinical rationale to support the combination of Hu5F9-G4 (magrolimab) with tumor-targeting monoclonal antibodies. While cancers appear to be more susceptible to CD47 blockade than normal cells, the efficacy of anti-CD47 antibodies can be augmented by combining with tumor-specific antibodies. Mouse xenograft models demonstrated a strong synergy between anti- CD47 and rituximab (Figure 4) (Chao *et al*., 2010a). The synergistic activity of CD47 blockade with tumor-targeting antibodies has now been validated by a phase 1b study combining Hu5F9-G4 (magrolimab) with rituximab in relapsed or refractory B-cell lymphomas (Figure 4) (Advani *et al*., 2018). In this 22-patient trial (15 patients with diffuse large B-cell lymphoma and 7 patients with follicular lymphoma), the ORR was 50% with 36% of patients having a CR. Notably, 95% of patients had disease that had been refractory to rituximab. Thus, Hu5F9-G4 (magrolimab) appears to synergize safely and effectively with tumor-specific monoclonal antibodies. Given the excellent safety data of mogamulizumab, it is very likely that the combination of mogamulizumab and Hu5F9-G4 (magrolimab) will be safe and well-tolerated.

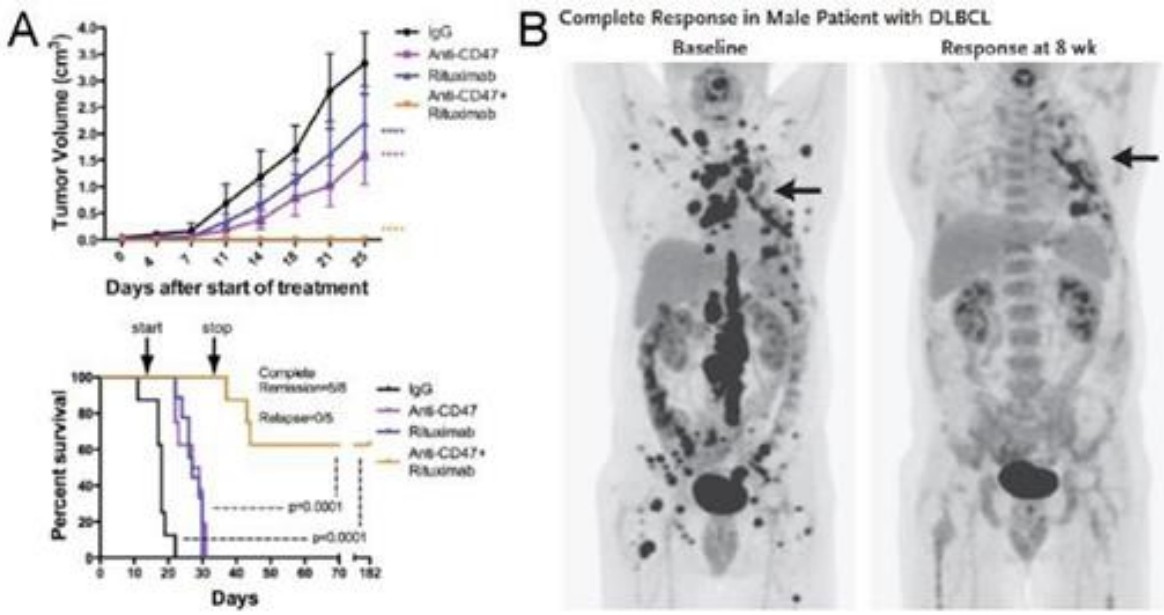


Figure 4: (A) NOD scid gamma (NSG) mice transplanted with Raji cells were treated with the indicated antibodies. Tumor volume is shown on top and Kaplan-Meier survival plots on bottom (Chao *et al*., 2010a). (B) positron emission tomography (PET) scan before and after Hu5F9-G4 (magrolimab) and Rituximab treatment in a patient with DLBCL (Advani *et al*., 2018)

2.4.3 Rationale For Use of Priming Dose for Hu5F9-G4 (magrolimab)

Because of the IgG4 isotype, Hu5F9-G4 (magrolimab) does not induce effective Fc-dependent effector functions. This results in reduced phagocytosis of normal cells, which lack expression of natural pro-phagocytic signals (Feng *et al.*, 2015). The exception to this is erythrocytes, which do acquire natural pro-phagocytic signals as they age. Blockade of CD47 with Hu5F9-G4 (magrolimab) causes a dose-dependent anemia due to the rapid clearance of aged erythrocytes (Sikic *et al*., 2019). Subsequently, a dose priming strategy has been adopted to mitigate this toxicity. This entails a single, subtherapeutic priming dose of Hu5F9-G4 (magrolimab) to induce clearance of older erythrocytes. This allows sufficient time to induce a compensatory reticulocytosis before the first full dose of Hu5F9-G4 (magrolimab) is given. This strategy appears to limit the degree and duration of anemia associated with Hu5F9-G4 (magrolimab) treatment (Figure 5).

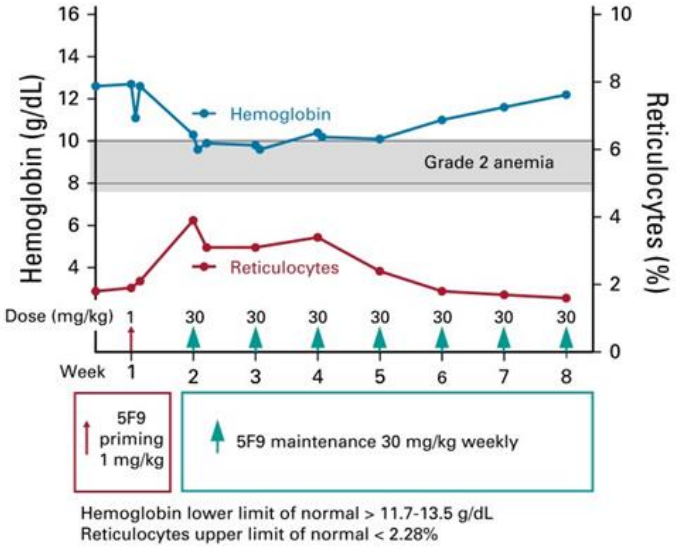


Figure 5: Anemia and reticulocyte kinetics with Hu5F9-G4 (magrolimab) priming strategy (Sikic *et al*, 2019)

2.4.4 Rationale for the proposed trial dosing schema

Analogous to the combination with rituximab, we hypothesize that Hu5F9-G4 (magrolimab) will have synergistic efficacy when combined with mogamulizumab in CCR4-expressing T-cell lymphomas. We also propose that the combination may be effective even in patients with prior mogamulizumab exposure based on the experience with rituximab and Hu5F9-G4 (magrolimab). The dosing schema proposed here follows the FDA-approved dosing for mogamulizumab. No dose-limiting toxicities (DLTs) were identified in the phase 1/2 study of mogamulizumab and the dose regimen was selected based on the PK profile of mogamulizumab. Because the mechanism of action of Hu5F9-G4 (magrolimab) synergy relies on a constant presence of pro-phagocytic signaling from the mogamulizumab Fc receptor, optimal efficacy will require continuous dosing. The phase 1b portion of this trial will aim to determine a safe dose of Hu5F9-G4 (magrolimab). We will target a dose of 30 mg/kg given every 2 weeks, which was been shown to be sufficient to achieve near 100% CD47 receptor occupancy (Figure 6). Because of the excellent safety profile of each individual drug, and the lack of synergistic toxicity seen in the combination trial with rituximab, we expect this combination to be safe and well-tolerated. Accordingly, we have selected a dose de-escalation design that will start at the target Hu5F9-G4 (magrolimab) dose of 30 mg/kg. If there is unacceptable toxicity at this dose, we will reduce the Hu5F9-G4 (magrolimab) dose to 20 mg/kg, which was shown to maintain excellent tumor penetrance into lymph nodes (Figure 6).

As of the July 2023 amendment, the phase 1b portion has been completed with an enrollment of 6 patients at dose level 1. Out of the 6 patients treated, 1 experienced a DLT. The recommended phase 2 dose (RP2D) has been established as dose level 1 (30mg/kg magrolimab starting cycle 1).

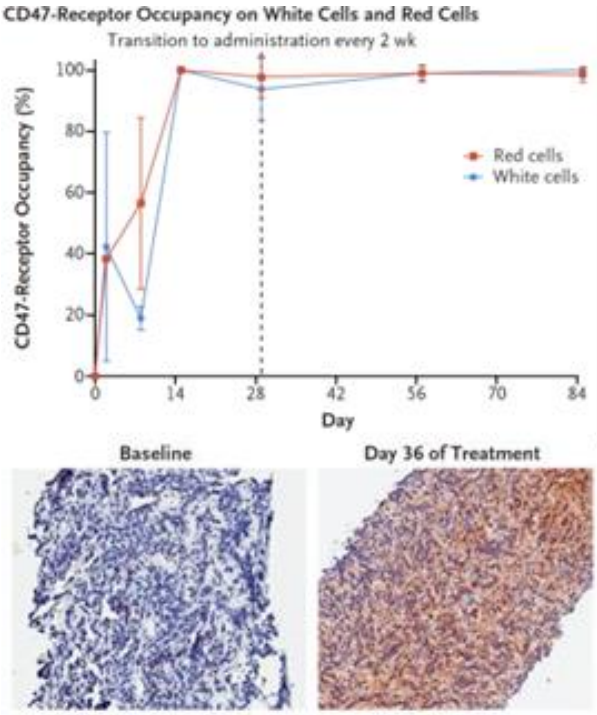


Figure 6: Top shows CD47 receptor occupancy on erythrocytes and leukocytes at a dose of 30 mg/kg every 2 weeks. Bottom shows detection of Hu5F9-G4 (magrolimab) in a malignant lymph node in a patient treated at a dose of 20 mg/kg. (Sikic *et al*., 2019)

2.4.5 Rationale for the primary endpoint in the primary phase 2 cohort

CTCL has unique symptoms, including disturbing visible and pruritic qualities that impact treatment decisions, complicating traditional trial endpoints, including ORR, PFS, and DOR. Objective responses with >50% reduction may not equal clinical benefit, and symptomatic patients often elect to transition to new therapy without objective progression, censoring them from PFS and DOR analysis. Meaningful impact of CTCL therapy should reflect both ORR and DOR without the initiation of new treatment. Therefore, composite endpoints that reflect both ORR and DOR are increasingly being explored in trials of CTCL (Kim *et al*., 2016). In this trial, we have selected the primary endpoint of ORR6, defined as the rate of objective responses lasting at least 6 months without the initiation of new therapy. Importantly, this new type of composite endpoint has been well-received by the FDA as a relevant endpoint for trials in CTCL. ORR4 (the rate of objective responses lasting at least 4 months without the initiation of new therapy) was the primary endpoint of the pivotal ALCANZA trial which lead to the FDA approval of brentuximab vedotin for the treatment of CD30-positive cutaneous T- cell lymphomas (Prince *et al*., 2017). We believe that for this patient population, which differs from that of the ALCANZA trial, a response duration of 6 months would be more clinically meaningful and important than the shorter ORR4 endpoint.

2.5 Correlative Studies Background

2.5.1 Integrated Correlative Study

2.5.1.1 CCR4 expression

2.5.1.1.1 Biologic rationale

Mogamulizumab is an anti-CCR4 antibody. The mechanism of action is believed to be through antibody dependent cell-mediated cytotoxicity and antibody dependent cellular phagocytosis. Thus, the efficacy of mogamulizumab with or without Hu5F9-G4 (magrolimab) will be dependent on CCR4 expression on the malignant T-cells. While the vast majority of MF and SS express CCR4, it is unknown whether loss of the CCR4 antigen may emerge as a resistance mechanism to mogamulizumab.

2.5.1.1.2 Hypothesis

Lymphomas with low or absent CCR4 expression will not respond to treatment with mogamulizumab or mogamulizumab plus Hu5F9-G4 (magrolimab).

2.5.1.1.3 Relevant preclinical and clinical data

Preclinical data relevant to this assay is discussed in Section 2.1.2.

2.5.2 Exploratory Correlative Studies

2.5.2.1 Spatial association of tumor cells and components of the tumor microenvironment including macrophage enumeration and phenotyping

2.5.2.1.1 Biologic rationale

The primary mechanism of action for Hu5F9-G4 (magrolimab) is believed to be through the promotion of phagocytosis by tumor-associated macrophages (TAMs). The infiltration of TAMs in the tumor microenvironment, their polarization phenotype, and their spatial proximity to CTCL cells in the skin are all potential biomarkers to both predict response to anti-CD47 therapy.

2.5.2.1.2 Hypothesis

A spatial signature of macrophages in the skin tumor microenvironment will be identified that will correlate with response to therapy with mogamulizumab plus Hu5F9-G4 (magrolimab).

2.5.2.1.3 Relevant preclinical and clinical data

Macrophages are a prominent component of the tumor microenvironment of CTCLs (Sugaya *et al*., 2012; Assaf and Hwang 2016; Wu *et al*., 2014). In particular, M2 macrophages have been reported to appear to be play an important role in CTCL progression (Sugaya *et al*., 2012; Wu *et al*., 2014; Furudate *et al*., 2016). Treatment with anti-CD47 antibodies have been shown to promote M1 macrophage polarization in murine glioblastoma models (Zhang *et al*., 2016).

2.5.2.2 Whole Exome Sequencing

2.5.2.2.1 Biologic rationale

Somatic mutations involving CCR4, the target of mogamulizumab, have been described in MF/SS. These mutations may affect the efficacy of the study drugs. Germline polymorphisms in CD47 signaling pathway members may also affect the efficacy of Hu5F9-G4 (magrolimab).

2.5.2.2.2 Hypothesis

C-terminal "gain-of-function" mutations of CCR4 will confer an improved ORR6. One or more polymorphisms in the CD47 pathway may be associated with improved ORR6.

2.5.2.2.3 Relevant preclinical and clinical data

CCR4 gain of function mutations are known to confer an improved outcome in ATLL (Sakamoto *et al.*, 2018). Subsequently, CCR4 mutations have been discovered CTCL (Wang *et al*., 2015). However, it is unknown whether these mutations will confer a similar improved outcome in response to mogamulizumab treatment in CTCL. Preclinical data has suggested that polymorphisms in SIRP may confer improved outcomes in response to CD47 therapy (Wong *et al.*, 2014). Similarly, polymorphisms in the Fc receptor genes may promote antibody-dependent clinical responses (Zhang *et al.*, 2007).

2.5.2.3 RNA Sequencing

2.5.2.3.1 Biologic rationale

Transcriptional profiles of CTCL have been shown to be prognostic. These transcriptomes may also yield a signature that could be predictive of response or resistance to CCR4/CD47 targeted therapy. Additionally, paired transcriptomes before treatment and at progression may elucidate novel molecular mechanisms of resistance.

2.5.2.3.2 Hypothesis

Transcriptome profiling of samples will reveal a gene signature that correlates with response to treatment with mogamulizumab plus Hu5F9-G4 (magrolimab).

2.5.2.3.3 Relevant preclinical and clinical data

Multiple studies have found prognostic gene expression signatures in CTCL patients (Litvinov *et al*., 2015; Litvinov *et al*., 2017). CCR4 gene expression has been shown to not only distinguish CTCL from benign skin biopsies, but also is prognostic (Litvinov *et al*., 2017).

2.5.2.4 Phagocytosis Index

2.5.2.4.1 Biologic rationale

T-cell lymphomas display marked variability in their susceptibility to phagocytosis in the presence or absence of CD47-blocking antibodies. An *in vitro* phagocytosis assay, with or without CD47-blocking antibodies may identify lymphomas with the highest phagocytic potential.

2.5.2.4.2 Hypothesis

Patients with the greatest phagocytic response to CD47 blockade in an *in vitro* assay may derive the greatest benefit from CD47-targeting therapy.

2.5.2.4.3 Relevant preclinical and clinical (if available) data

It has been shown that T-cell lymphomas are not effectively targeted by CD47-blocking antibodies that lack a functional Fc, but that addition of a tumor-targeting antibody such as mogamulizumab can synergize with CD47 blockage (Jain *et al.*, 2019). Primary T-cell lymphomas intrinsically vary greatly in their susceptibility to CD47 blockade *in vitro*, but it is unknown whether performance in an *in vitro* assay of phagocytosis will correlate with clinical activity.

2.5.2.5 Immunophenotyping of circulating tumor cells

2.5.2.5.1 Biologic rationale

Levels of expression of CCR4 and CD47 may correlate with responses to therapy with mogamulizumab plus Hu5F9-G4 (magrolimab). Because a significant proportion of patients are anticipated to have circulating leukemic disease, we can phenotype circulating tumor cells to measure the expression of these markers, and to also estimate the fraction of other potentially relevant immune populations in the blood such as monocytes.

2.5.2.5.2 Hypothesis

Low CCR4 and/or CD47 expression on circulating Sezary cells will be correlated with worse clinical outcomes.

2.5.2.5.3 Relevant preclinical and clinical data

While the expression of CCR4 can vary greatly on circulating Sezary cells (Duvic *et al*., 2015), it is unclear whether higher levels of expression may correlate with improved clinical responses. Additionally, mogamulizumab has been shown to reduce the number of circulating regulatory T-cells (Ni *et al*., 2015). It is possible that the combination of mogamulizumab plus Hu5F9-G4 (magrolimab) may be more potent in clearing regulatory T-cells.

2.5.2.6 T cell receptor sequencing

2.5.2.6.1 Biologic rationale

High throughput sequencing of the T-cell receptor is a more sensitive and specific method to track minimal residual disease (MRD) in patients with T-cell lymphoma.

2.5.2.6.2 Hypothesis

Patient with the greatest reduction in MRD or with undetectable MRD after treatment will have a higher ORR6 and greater duration of response.

2.5.2.6.3 Relevant preclinical and clinical data

TCR sequencing has emerged as a powerful tool to sensitively and specifically track CTCL cells in skin and blood (Kirsch *et al.*, 2015). Minimal residual disease monitoring by TCR sequencing has correlated with outcomes in the setting of allogeneic stem cell transplantation (Weng *et al.*, 2013).

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Diagnosis of either MF or SS by the World Health Organization (WHO) 2016 classification (Swerdlow *et al*., 2017), stage IB-IV by modified International Society for Cutaneous Lymphomas (ISCL)/ European Organization of Research and Treatment of Cancer (EORTC) classification (Olsen *et al*., 2011), without large cell transformation (LCT) at the time of screening. Patients with a history of prior LCT are permitted.

3.1.2 Patients must have had at least one prior course of systemic therapy.

3.1.3 Age ≥18 years.

Because no dosing or adverse event data are currently available on the use of Hu5F9-G4 (magrolimab) in combination with mogamulizumab in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.4 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.5 Patients must have adequate organ and marrow function as defined below:

– Hemoglobin	≥9.5 g/dL and transfusion independence (defined as not requiring more than 2 units of red blood cell (RBC) transfusions during the 4-week period prior to screening)
– absolute neutrophil count	≥1,000/mcL
– platelets	≥75,000/mcL
– total bilirubin	≤1.5 × institutional upper limit of normal (ULN)

	except for subjects with Gilbert's syndrome or genetic equivalent
– AST(SGOT)/ALT(SGPT)	≤3 × institutional ULN
– glomerular filtration rate (GFR)	≥40 mL/min/1.73 m^2 by the Cockcroft-Gault formula (see Appendix B)

3.1.6 Patients must meet the following minimum wash-out window from previous treatments to the first treatment

- ≥3 weeks for systemic anti-cancer therapies
- ≥2 weeks for phototherapy, local radiation therapy, topical high potency corticosteroid, topical retinoid, topical nitrogen mustard, or topical toll-like receptor (TLR)-agonist
- ≥12 weeks for total skin electron beam therapy

Participants with rapidly progressive malignant disease may be enrolled prior to completion of the above periods with approval of the protocol director.

3.1.7 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.1.8 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.9 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.10 Patients with **treated brain metastases** are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression for a minimum of 3 months.

3.1.11 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.1.12 The effects of Hu5F9-G4 (magrolimab) on the developing human fetus are unknown. For this reason and because monoclonal antibody agents as well as other therapeutic agents used in this trial (mogamulizumab) are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation and continue for 4 months after the last dose of both Hu5F9-G4 (magrolimab) and mogamulizumab. Effective contraception is defined as oral contraceptives, double barrier method (condom plus spermicide or diaphragm plus spermicide) or practice true abstinence from heterosexual intercourse. Women of childbearing potential includes any female who has experienced menarche and has not undergone successful surgical sterilization or is not postmenopausal (defined as

amenorrhea ≥12 consecutive months). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol who are sexually active with women of childbearing potential and who have not had vasectomies must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of Hu5F9-G4 (magrolimab) administration.

3.1.13 Female patients of childbearing potential must not be nursing or planning to be pregnant and must have a negative urine or serum pregnancy test within 30 days before randomization and within 72 hours before the first administration of study treatment.

- Female patients of childbearing potential must be willing to use one highly effective method of contraception during the study and continue for 4 months after the last dose of study treatment.

- Male patients who are sexually active with a woman of childbearing potential (WOCBP) and who have not had vasectomies must be willing to use a barrier method of contraception (condom plus spermicidal gel) and refrain from sperm donation during the study and for 4 months after the last dose of study treatment. 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 study treatment to prevent fetal exposure to study treatment.

3.1.14 Ability to understand and the willingness to sign a written informed consent document. Participants with impaired decision-making capacity (IDMC) who have a legally-authorized representative (LAR) and/or family member available will also be eligible.

3.1.15 Willing to comply with clinic visit schedule and procedures including mandatory biopsies

3.2 Exclusion Criteria

3.2.1 Prior treatment with Hu5F9-G4 (magrolimab) or any agent targeting CD47-SIRPα

3.2.2 Prior progression of disease with mogamulizumab

3.2.3 Patients who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1) with the exception of alopecia and lymphopenia (any grade permitted). Residual peripheral neuropathy must have improved to grade 2 or better.

3.2.4 Patients who are receiving any other investigational agents.

3.2.5 Allogeneic hematopoietic stem cell transplant recipients with any graft-versus-host disease within the previous 3 months or requiring immunosuppression

3.2.6 Active autoimmune disease that has required systemic immunosuppressive medication within the previous 3 months

3.2.7 Active herpes simplex or herpes zoster. Subjects on prophylaxis for herpes who have no active signs of active infection, and whose last active infection was more than 6 months ago, may enter the study, and should continue to take the prescribed medication for the duration of the study

3.2.8 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Hu5F9-G4 (magrolimab), other monoclonal antibodies, or other agents (mogamulizumab) used in study.

3.2.9 Significant cardiopulmonary disease defined as
   a. Acute myocardial infarction within the last 6 months
   b. Unstable angina
   c. Congestive heart failure NYHA Class III-IV

3.2.10 Patients with uncontrolled intercurrent illness requiring antibiotics. Patients on prophylactic antibiotics for non-complicated staphylococcus colonization/infection are eligible.

3.2.11 Patients with **new or progressive brain metastases** (active brain metastases) or **leptomeningeal disease** are excluded.

3.2.12 Patients with psychiatric illness/social situations or substance abuse that would limit compliance with study requirements.

3.2.13 Pregnant women are excluded from this study because Hu5F9-G4 (magrolimab) is monoclonal antibody agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Hu5F9-G4 (magrolimab), breastfeeding should be discontinued if the mother is treated with Hu5F9-G4 (magrolimab). These potential risks may also apply to other agents used in this study (mogamulizumab).

3.2.14 Patients with RBC transfusion dependence, defined as requiring more than 2 units of RBCs transfused during the 4-week period prior to screening. RBC transfusions are permitted during the screening period and prior to enrollment.

3.2.15 Patients with prior autoimmune thrombocytopenia, hemolytic anemia or Evans Syndrome requiring treatment in the last 12 months.

3.2.16 Patients on the following medications at the time of enrollment:
- Immunotherapy or immunosuppressive drugs (e.g. chemotherapy or systemic corticosteroids) EXCEPT for the following:
   - Intranasal, inhaled, or local steroid injection (e.g. intra-articular injection)
   - Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or

equivalent, if patient has been on a stable dose for at least 2 weeks prior to the first treatment
    - Low and medium potency topical corticosteroids are permitted if patient has been on a stable dose for at least 2 weeks prior to the first treatment
    - Steroids as premedication for hypersensitivity reactions (e.g. CT scan premedication).
- Growth factors (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor) EXCEPT for erythropoietin and darbepoietin alpha.
- Herbal remedies with immunostimulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (e.g. hypericin).

3.2.17 Live vaccines are not allowed while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), typhoid (oral) vaccine, and intranasal influenza vaccines (*e.g.*, Flu-Mist®). However, seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr/. The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- Investigator (IVR): MD, DO, or international equivalent,
- Non Physician Investigator (NPIVR): advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- Associate Plus (AP): clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges,
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN,
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval, and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status,
- Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster,
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record,
- Include the IRB number of the IRB providing approval in the FDA Form 1572 in the RCR profile,
- List all sites on the IRB/REB approval as Practice Sites in the FDA Form 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federalwide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO),
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

4.2.1 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org)
- Click on *Protocols* in the upper left of the screen

  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select LAO-CA043, and protocol number 10384,
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration*, to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.2 Protocol Specific Requirements For 10384 Site Registration

- Specimen Tracking System Training Requirement:
  - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
  - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
  - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. Users are strongly encouraged to take a refresher of the training if they have not entered specimen data for an extended period of time.
  - This training will need to be completed before the first patient enrollment at a given site.
  - Please contact STS Support at Theradex for the training (STS.Support@theradex.com).

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal, log on to the CTSU members' website, go to the Regulatory section, and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific DTL using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing

the DTL are available in the Help Topics button in the DTL application and describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List.

4.2.4 Checking Site Registration Status

Site's registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen
- Click on *Site Registration , and*
- Enter the site's 5-character CTEP Institution Code and click on Go
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN or IWRS will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their FDA Form 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. IWRS system also sends an email confirmation of the registration. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with patient enrollment in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System or the IWRS Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

4.3.2 Special Instructions for Patient Enrollment

1. Site staff with the appropriate roles will reserve slots using IWRS (https://open.ctsu.org/).
2. City of Hope Cancer Center will receive notification via the IWRS when a slot has been reserved. An e-mail will be sent from the City of Hope Cancer Center to the site requesting further information such as: patient initials, tumor type, and potential start date. The spot will show as 'pending approval' in the system until the site sends a REGISTRATION FORM/ELIGIBILITY CHECKLIST accompanied with documents supporting eligibility (signed consent, baseline labs, pathology reports, bone marrow reports, CT or x-ray reports, and latest clinic note) to the City of Hope Cancer Center at ccc@coh.org for review and confirmation of eligibility.
3. Once the registration has been reviewed, the City of Hope Cancer Center will either approve or disapprove the request depending on confirmation of patient eligibility. If approved, the City of Hope Cancer Center will update the spot to 'reserved' in IWRS.
4. The site can now enroll the patient into the study in OPEN.

This Study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through Rave user roles: "Rave CRA" and "Rave CRA (Labadmin)"for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank, formerly known as the ETCTN Biorepository).

- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website in the Data Management section under the Rave Home tab and then under Rave Resource Materials.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions on use of the STS can be found in Section 5.3.

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN link of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 855-828-6113 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 7 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Time Point	Specimen	Send Specimens To:
Archival		
	• Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred)[1] (optional) If a block is not available, then submit (optional): • 1 H&E stained slide (3-5 µm) • 5 unstained, charged slides (3-5 µm) • 30 unstained, uncharged, air-dried slides (10 µm)	EET Biobank
Baseline		

	• 2 skin punches ≥5mm in formalin (mandatory[2,3]) • 80 mL whole blood in Sodium Heparin Green Top Tubes (mandatory) • 3 mL whole blood in a Red Top Tube, processed to serum and frozen (mandatory)	EET Biobank
Cycle 1 Week 2		
	• 2 skin punches ≥5mm diameter in formalin (mandatory[2,3]) • 20 mL whole blood in Sodium Heparin Green Top Tubes (mandatory) • 3 mL whole blood in a Red Top Tube, processed to serum and frozen (mandatory)	EET Biobank
Cycle 3 Week 3		
	• 2 skin punches ≥5mm diameter in formalin (mandatory[2,3]) • 20 mL whole blood in Sodium Heparin Green Top Tubes (mandatory) • 3 mL whole blood in a Red Top Tube, processed to serum and frozen (mandatory)	EET Biobank
Cycle 6 Week 1		
	• 20 mL whole blood in Sodium Heparin Green Top Tubes (mandatory) • 3 mL whole blood in a Red Top Tube, processed to serum and frozen (mandatory)	EET Biobank
End of Treatment or Progression		
	• 2 skin punches ≥5mm diameter in formalin (mandatory[2,3]) • 20 mL whole blood in Sodium Heparin Green Top Tubes (mandatory) • 3 mL whole blood in a Red Top Tube, processed to serum and frozen (mandatory)	EET Biobank

[1]For archival tissue, a copy of the corresponding anatomic pathology report must be sent with the tissue and uploaded to Rave. If submitting slides, then slides must be processed in order, and numbered sequentially (*e.g.*, H&E stained slide is created first and labeled 1, unstained slides are then created and numbered 2 – n).
[2]Skin biopsies are not required if the patient does not have active skin lesions at the designated timepoint (*e.g.* patients with a complete response in the skin compartment).
[3]For new biopsies, the Tissue Biopsy Verification Form (Appendix D) and a copy of the radiology and/or operative reports from the tissue removal procedure and the diagnostic

anatomic pathology report must be sent with the tissue to the EET Biobank.

5.2 Specimen Procurement Kits and Scheduling

5.2.1 Specimen Procurement Kits

Kits for the collection and shipment of skin punches in formalin to the EET Biobank can be ordered online via the Kit Management system: (https://kits.bpc-apps.nchri.org/).

Users at the clinical sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Please note that protocol may include more than one type of kit. Each user may order two kits per kit type per day (daily max = 6 kits). Kits are shipped ground, so please allow 5-7 days for receipt. A complete list of kit contents for each kit type is located on the Kit Management system website.

Note: Kits or supplies are only provided for specimens shipped to the Biobank. Institutional supplies must be used for all other specimen collection and processing.

5.2.2 Scheduling of Specimen Collections

Please adhere to the following guidelines when scheduling procedures to collect tissue:

- Tumor tissue specimens collected during biopsy procedures and fixed in formalin must be shipped on the same day of collection.
- Tissue in formalin can be collected Monday through Wednesday and shipped overnight for arrival on Tuesday through Thursday at the EET Biobank at Nationwide Children's Hospital.
- Fresh blood specimens may be collected and shipped Monday through Friday.
- Specimens submitted frozen (*e.g.* serum) can be collected on any day but must be stored frozen and shipped to the EET Biobank on Monday through Thursday. In the event that frozen specimens cannot be shipped immediately, they must be maintained in a -70°C to -80°C freezer.

5.3 Specimen Tracking System Instructions

5.3.1 Specimen Tracking System Overview and Enrollment Instructions

For the ETCTN STS, the following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements:

- Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this or any other protocol that uses the ETCTN Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies, the radiology and operative report(s) must also be uploaded into Rave. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, date of birth, initials, medical record number, and patient contact information from the institutional pathology report prior to submission.**

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact STS Support at STS.Support@theradex.com.

The Shipping List report **must** be included with all sample submissions.

5.3.2 Specimen Labeling

5.3.2.1 Blood Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, serum)
- Collection date (to be added by hand)

5.3.2.2 Tissue Specimen Labels

Include the following on all tissue specimens or containers (*e.g.*, formalin jar):

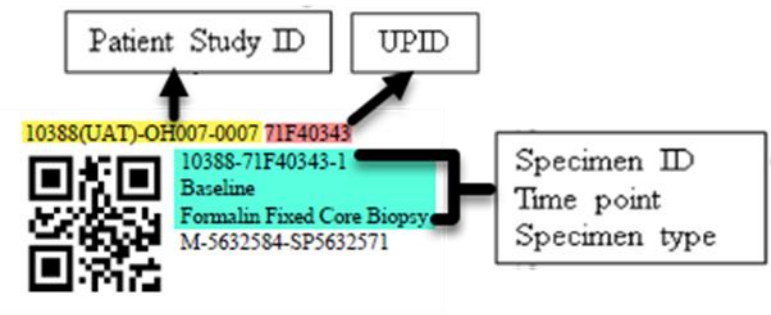
- Patient Study ID
- Universal Patient ID (UPID)

- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, formalin-fixed paraffin-embedded [FFPE] Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Biopsy site
- Surgical pathology ID (SPID) number (when applicable)
- Block number from the corresponding pathology report (archival only)
- Collection date and time (to be added by hand)
- Slide section number (only if archival tissue is submitted as slides) (to be added by hand)

5.3.2.3 Example of Specimen Label Generated by STS

STS includes a label printing facility, accessed via the Print Label CRF in the All Specimens folder. A generated PDF is emailed to the user as a result of saving that form.

The following image is an example of a tissue specimen label printed on a label that is 0.5" high and 1.28" wide.



The QR code in the above example is for the Specimen ID shown on the second line.

Labels may be printed on a special purpose label printer, one label at a time, or on a standard laser printer, multiple labels per page. Theradex recommends the use of these low temperature waterproof labels for standard laser printers: https://www.labtag.com/shop/product/cryo-laser-labels-1-28-x-0-5-cl-23-colors-available/

The last line item on the label includes the following data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. An optional alpha-numeric code that is protocol specific and is only included if the protocol requires an additional special code classification

Space is provided at the bottom of the label for the handwritten date and optional time. The last line on the example label is for the handwritten date and optional time.

5.3.3 Overview of Process at Treating Site

5.3.3.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization, and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

5.3.3.2 Rave Specimen Tracking Process Steps

Step 0: Log into Rave via your CTEP-IAM account, then navigate to the appropriate participant.

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, and number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using the Print Labels CRF located in the All Specimens folder, then and collect specimen.

- Label specimen containers and write collection date *[if the study also requires recording the collection time on the label, include the time]* on each label. After collection, store labeled specimens as described in Section 5.3.2.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), Surgical (or Operative) reports and Tissue Biopsy Verification form (when applicable). Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per

specimen). Uploaded reports should have protected health information (PHI) data, like name, date of birth, mailing address, medical record number or social security number (SSN), redacted. Do not redact SPID, block number, diagnosis, or relevant dates (such as collection date), and include the UPID and patient study ID on each document (either by adding a label or hand writing).

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form: Enter collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of sample containers and ship date once for the first specimen in a shipment.
- **Copy Shipping** CRF: In the specimen folders for additional specimens (if any) that will be shipped with the initial specimen, please use the **Copy Shipping** form to derive common data into additional **Shipping Status** forms. A few unique fields will still need to be entered in **Shipping Status.**

Step 5: Print shipping list report and prepare to ship.

- Shipping List report is available at the site level.
- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

Step 8: Monitor the Receiving Status form located in each specimen folder for acknowledgment of receipt and adequacy.

5.4 Specimen Collection

5.4.1 Archival or Formalin-Fixed Paraffin-Embedded (FFPE) Tumor Specimen

If previously-collected FFPE tissue will be submitted, then the following criteria must be met:

- Tissue must have been collected within 6 months prior to registration or any time after registration
- FFPE tumor tissue block(s) must be submitted. The optimal block is at least 70% tumor. Specimen size requirement is as follows:
    - Surface area: 25 mm^2 is optimal. Minimum is 5 mm^2.
    - Volume: 1 mm^3 optimal. Minimum volume is 0.2 mm^3, however the success of

DNA extraction decreases at suboptimal tissue volume.

If an existing block cannot be submitted, the following are requested, if available:

- One (1) H&E slide (3-5 µm)
- Five (5) 3-5 µm unstained air-dried charged slides
- Thirty (30) 10 µm unstained air-dried uncharged slides

Process and number slides sequentially (e.g., H&E stained slide should be created first and labeled with "1," and additional unstained slides should be processed next and be labeled 2 – n).

See Section 5.3.2 for labeling instructions.

5.4.2 Formalin-Fixed Skin Punch Biopsies

1. Label formalin-filled containers according to instructions in Section 5.3.2.
2. Obtain two ≥5mm punch biopsies, and place one punch in each cassette.
3. Snap the cassette lids closed and place cassettes into pre-labeled container(s) (one container per biopsy site) filled with 10% neutral buffered formalin as soon as possible after collection to prevent air drying. Samples should be fixed for 3-72 hours.
4. Secure the container lids and package containers into the shipping kit according to instructions in Section 5.5. Keep tissue in formalin jars at room temperature until shipment to the EET Biobank.

5.4.3 Blood Collection

5.4.3.1 Collection of Blood in Sodium Heparin Tubes for Whole Blood Processing

1. Label Sodium Heparin tubes according to the instructions in Section 5.3.2.
2. Collect specified volume of blood per timepoint (see Section 5.1) in Sodium Heparin tubes and gently invert tubes to mix.
3. Ship on day of collection (whenever possible) according to instructions in Section 5.5.
4. If blood cannot be shipped on the day of collection (e.g., a late scheduled collection), then refrigerate until shipment.

5.4.3.2 Collection of Blood in Red Top Tubes for Serum Processing

1. Collect specified volume of blood per timepoint (see Section 5.1) in a Red Top Serum tube and gently invert tubes 8-10 times to mix.
2. Place the Red Top tube upright. Allow 30 minutes of clotting time at room temperature.
3. Centrifuge Red Top tube for 10-15 minutes at 1,000-1,300 RCF (g) in a swing bucket centrifuge.
4. Label cryovials according to the instructions in Section 5.3.2.
5. Transfer equal aliquots of the serum layer to 4 cryovials.
6. Cap cryovials and place immediately upright on ice. Freeze immediately at -70˚ or

colder until shipment.

5.5 Shipping Specimens from Clinical Site to the EET Biobank

5.5.1 General Shipping Information

Skin punch biopsies that are fixed in formalin and fresh blood should be shipped at ambient temperature the day of collection. For skin punch biopsies, the Tissue Biopsy verification form is required both in the package and uploaded in the ETCTN specimen tracking system. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container.

For all archival tissue, the corresponding anatomical clinical pathology report is required both in the package and uploaded in the ETCTN specimen tracking system. If this is not available at the time of shipment, then it must be sent to the EET Biobank as soon as possible and uploaded to the ETCTN specimen tracking system, or the specimen will not be processed. The pathology report must state the disease diagnosis made by the reviewing pathologist.

5.5.1.1 Required Forms for Specimen Submissions:

Each document submitted with the specimen must be labeled with a label printed from the STS, or the Universal ID and Patient Study ID.

Tissue	**Required Forms**
Archival	1. Shipping List 2. Corresponding Pathology Report
Skin punch biopsies in formalin	1. Shipping List 2. Tissue Biopsy Verification Form 3. Diagnostic Pathology Report 4. Surgical and/or Radiology Report
Blood	1. Shipping List

5.5.2 Specimen Shipping Instructions

Tissue in formalin must be shipped on the day of collection. Collect and ship on Monday through Wednesday.

Frozen specimens and archival (FFPE) tissue may be shipped on Monday through Thursday.

Fresh blood may be shipped on Monday through Friday. Please select “Saturday Delivery” when shipping fresh blood on a Friday.

5.5.2.1 Shipping of FFPE Blocks and Glass Slides

1. Before packaging blocks or slides, verify that each specimen is labeled according to Section 5.3.2.2.
2. Blocks should be placed in a hard-sided container, preferably a special block holder, to protect the specimen. Glass slides are to be placed in plastic slide holders. Place tissue paper on top of the separated slides prior to closing the slide holder to reduce slide movement during shipment.
3. Place the blocks or slides in a reinforced cardboard shipping box with appropriate packaging filler to minimize movement of specimens within the shipping box.
4. Include a copy of the forms listed above and a shipping manifest from the Specimen Tracking System with each shipment.
5. Please include a cold pack when shipping on hot days and extra insulation on cold days.

Ship specimens to the address listed below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.5.2.2 Shipping Ambient Blood Using Institutional Supplies (kits are not provided).

1. Before packaging specimens, verify that the collection tube is labeled according to instructions in section 5.3.2.1.
2. Place the blood collection tube into a zip-lock bag.
3. Place zip-lock bag into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
4. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
5. Place the specimen(s) and a copy of the shipping manifest into a sturdy shipping container. In winter months, please use an insulated container and include extra insulation, such as bubble wrap, inside the shipping container to prevent specimens from freezing.
6. Close the container and tape shut.
7. Attach a shipping label to the top of the shipping container.
8. Attach an Exempt Human Specimen sticker to the side of the container.
9. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.5.2.3 Shipping Frozen Specimens Using Supplies Provided by the Institution

1. Before packaging specimens, verify that each specimen is labeled according to the instructions in 5.3.2 and that lids of all primary receptacles containing liquid are tightly sealed.
2. Place the specimens in zip-lock bags. Use a separate zip-lock bag for each specimen type and time point.
3. Place the zip-lock bags in a biohazard envelope containing absorbent material. Expel as much air as possible and seal securely.

4. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
5. Place frozen specimens into the insulated shipping container with dry ice. Layer the bottom of the container with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the container is almost completely full. When packaging specimens, ensure that you leave enough room to include at least 5 pounds of dry ice in the shipment.
6. Insert a copy of the required forms into a plastic bag and place in the shipping container.
7. Close the shipping container and tape it shut with durable sealing tape. Do not completely seal the container.
8. Complete a FedEx air bill and attach to top of shipping container.
9. Complete a dry ice label.
10. Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
11. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.5.2.4 Shipping Ambient Tissue and Blood in a Single-Chamber Kit

Blood in sodium heparin may be shipped in the kit with the tissue in formalin when collected on the same day.

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above Section 5.3.2 and that the lids of all primary receptacles containing liquid are tightly sealed. The lids of formalin jars should be wrapped in parafilm. Absorbent material must be placed around each primary container that holds liquid.
2. Place the specimens in zip-lock bags. Use a separate bag for each specimen type.
3. Place specimens into the secondary pressure vessel surrounded by bubble wrap. Place the lid on the secondary pressure vessel and set it inside the kit chamber.
4. Place a copy of the shipping manifest and corresponding reports such as pathology, surgical, or radiology reports into the insulated shipping container.
5. Set the lid on top of the container. Close the outer flaps and tape shut.
6. Attach a shipping label to the top of the shipping container.
7. Attach an Exempt Human Specimen sticker to the side of the container.
8. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.5.3 Shipping Address

Ship to the address below. Ship formalin-fixed and fresh blood specimens the same day of specimen collection. Do not ship specimens the day before a holiday.

EET Biobank
The Research Institute at Nationwide Children's Hospital
700 Children's Drive, WA1340

Columbus, Ohio 43205
PH: (614) 722-2865
FAX: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred.

NOTE: The EET Biobank FedEx Account will not be provided to submitting institutions. There is no central courier account for this study. Sites are responsible for the cost of shipments to the EET Biobank.

5.5.4 Contact Information for Assistance

For all queries, please use the contact information below:

EET Biobank
Toll-free Phone: (800) 347-2486
E-mail: BPCBank@nationwidechildrens.org

5.6 Biomarker Plan

Note for participating sites: Please see Section 5.1 for details on specimens to collect. The specimens tested are not always the same specimens that are submitted by the site, as processing of blood and tissue will occur at the Biobank prior to testing.

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Tissue-based Biomarkers							
1	CCR4 expression	Leica Bond-III automated stainer/Immunohistochemistry chromogenic CLIA: N	Integrated Purpose: Correlate pre-treatment CCR4 expression with responses	Unstained slides from archival tissue and skin biopsies	Archival,* Baseline, Cycle 1 Week 2, Cycle 3 Week 3, end of treatment or Progression	O (Archival) M (All other timepoints)	MSKCC Pathology Ahmet Dogan, M.D., Ph.D. dogana@mskcc.org
2	Spatial association of tumor cells and components of the tumor microenvironment including macrophage enumeration and phenotyping	CODEX imaging CLIA: N	Exploratory Purpose: Hypothesis generating Will evaluate expression and spatial distribution of key molecules including CD47 expression and cell populations in the tumor microenvironment, including macrophages	FFPE blocks from Archival tissue and skin biopsies Tissue collected for CCR4 expression assay will be used	Archival,* Baseline, Cycle 1 Week 2, Cycle 3 Week 3, end of treatment or Progression	O	Nolan Laboratory, Stanford University Garry Nolan, Ph.D. gnolan@stanford.edu

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
3	Whole Exome Sequencing	NGS CLIA: N	Exploratory Purpose: Hypothesis generating Will assess whether there is a trend towards improved responses to treatment with CCR4 gain-of-function mutations; whether other CCR4 mutation may confer primary or secondary resistance, whether SIRPA/FcR polymorphisms associate with improved responses, whether CD47 mutations may emerge on therapy	DNA from archival tissue and skin biopsies Tissue collected for CCR4 expression assay will be used	Archival*, Baseline and end of treatment or Progression Baseline time points will be used preferentially over archival samples.	O	NCLN Genomics Laboratory Mickey Williams, Ph.D. mickey.williams@nih.gov

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
4	RNAseq	NGS CLIA: N	Exploratory Purpose: Hypothesis generating Will evaluate for gene expression signature that correlates with response	RNA from archival tissue and skin biopsies Tissue collected for CCR4 expression assay will be used	Baseline and end of treatment or Progression	O	NCLN Genomics Laboratory Mickey Williams, Ph.D. mickey.williams@nih.gov
Blood-based Biomarkers							
1	Whole Exome Sequencing	NGS CLIA: N	Exploratory Germline Control	CD4-depleted PBMCs	Baseline or time of lowest peripheral blood Sezary cell percentage	M	NCLN Genomics Laboratory Mickey Williams, Ph.D. mickey.williams@nih.gov Khodadoust Laboratory (CD4 depletion) Michael Khodadoust MD PhD mkhodado@stanford.edu

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
2	Phagocytosis Index	In vitro phagocytosis assay of Sezary cells +/- Hu5F9-G4 (magrolimab)/moga CLIA: N	Exploratory Purpose: Hypothesis generating Will evaluate phagocytic activity of macrophages upon co-culture with Sezary cells +/- Hu5F9-G4 (magrolimab) +/- moga	PBMCs	Baseline and end of treatment or Progression	M; May only be performed on pretreatment samples containing sufficient proportion of circulation Sezary cells	Weinstock Laboratory, Dana-Farber Cancer Institute David Weinstock MD and Salvia Jain MD Davidm_weinstock@dfci.harvard.edu ssjain@bidmc.harvard.edu
3	Immunophenotyping of circulating tumor cells	CyTOF CLIA: N	Exploratory Purpose: Hypothesis generating Will perform high dimensional phenotyping of Sezary cells by CyTOF or else high dimensional flow cytometry. Will include expression of CCR4 and CD47	PBMCs	Baseline and end of treatment or Progression	M; May only be performed on pretreatment samples containing sufficient proportion of circulation Sezary cells	Khodadoust Laboratory and Stanford HIMC Michael Khodadoust MD PhD mkhodado@stanford.edu

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
4	T cell receptor sequencing	ClonoSeq CLIA: N	Exploratory Purpose: Hypothesis generating Will detect molecular residual disease before and during treatment	Whole blood or PBMCs	Baseline, Cycle 1 Week 2, Cycle 3 Week 3, Cycle 6 Week 1, end of treatment or Progression	M	Adaptive Biotechnologies
5	Anti-drug antibodies	Competition ELISA CLIA: N	Exploratory Purpose: Correlate development of ADA to Hu5F9-G4 (magrolimab) to clinical responses	Serum	Baseline, Cycle 1 Week 2, Cycle 3 Week 3, Cycle 6 Week 1, end of treatment or Progression	M	Gilead

5.7 Integrated Correlative Studies

5.7.1 CCR4 expression

5.7.1.1 Specimen(s) Receipt and Processing at the EET Biobank

EET Biobank will receive skin punch biopsy fixed in formalin at baseline, Cycle 1 Week 2, Cycle 3 Week 3, and end of treatment or progression. Samples should be processed to FFPE blocks within 72 hours of fixation. Five unstained sections, 3-4 micron, on charged slides will be used for this assay.

5.7.1.2 Site(s) Performing Correlative Study

This assay will be performed at MSKCC Pathology under the supervision of Ahmet Dogan, M.D., Ph.D. Archival tissue may be analyzed if available, but this does not replace the analysis of the formalin fixed skin biopsies collected at baseline, Cycle 1 Week 2, Cycle 3 Week 3, and end of treatment or progression.

5.7.1.3 Contact information for notification of specimen shipment

MSKCC Pathology
Ahmet Dogan, M.D., Ph.D.
dogana@mskcc.org

5.8 Exploratory/Ancillary Correlative Studies

5.8.1 Spatial association of tumor cells and components of the tumor microenvironment including macrophage enumeration and phenotyping

5.8.1.1 Specimen(s) Receipt and Processing at the EET Biobank

EET Biobank will receive skin punch biopsy fixed in formalin at baseline, Cycle 1 Week 2, Cycle 3 Week 3, and end of treatment or progression. Samples should be processed to FFPE blocks within 72 hours of fixation. Blocks should be shipped to the Nolan Laboratory after slides have been cut for the CCR4 expression assay (see Section 5.7.1).

5.8.1.2 Site(s) Performing Correlative Study

This assay will be performed at Nolan Laboratory, Stanford University, under the supervision of Garry Nolan, Ph.D.

5.8.1.3 Contact information for notification of specimen shipment

Nolan Laboratory, Stanford University
Garry Nolan, Ph.D.

5.8.2 Whole Exome Sequencing

5.8.2.1 Specimen(s) Receipt and Processing at the EET Biobank

FFPE tissue blocks will be sectioned to generate an initial hematoxylin and eosin (H&E)-stained slide. All H&E stained slides will undergo a pathology QA review and annotation for macrodissection. Following macrodissection, tumor tissue from unstained slides will be scraped for co-extraction of DNA and RNA. The nucleic acids will be analyzed to determine concentration and quality. DNA will be shipped to the central sequencing laboratory for analysis.

For collection of germline DNA, blood will be collected in Green Top tubes at baseline or at the time of lowest peripheral blood Sezary cell percentage. Samples should be processed by Ficoll gradient purification to isolate PBMCs. PBMCs will be cryopreserved in cryovials and stored in liquid nitrogen vapor phase freezer. Cryopreserved PBMCs collected at baseline or at the time of the lowest leukemic disease will be shipped from the EET Biobank to the Khodadoust laboratory. CD4 depletion will be performed at the Khodadoust Laboratory, Stanford University, under the supervision of Michael Khodadoust, M.D. Ph.D. PBMCs will be depleted of CD4-expressing cells and DNA will be extracted. DNA will be quantitated, and then stored in a -80°C freezer until shipping to the NCLN Genomics Laboratory for analysis.

5.8.2.2 Site(s) Performing Correlative Study

This assay will be performed at the NCLN Genomics Laboratory under the supervision of Mickey Williams, Ph.D.

5.8.2.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

DNA will be shipped from the EET Biobank to:

NCLN Genomics Laboratory at The University of Texas MD Anderson Cancer Center
Attn: Jincy Veliyathu or Khushali Rajendra Patel
Zayed Building
CTLU Z3.4020
6565 MD Anderson Blvd
Houston, TX 77030

Blood Specimens will be shipped from the EET Biobank to:

Stanford University/Khodadoust Laboratory
Attn: George Duran
1701 Page Mill Road, Suite #271
Palo Alto, CA 94304
650-725-6420
georgedu@stanford.edu

5.8.2.4 Contact information for Notification of Specimen Shipment

DNA and Blood: Thomas Forbes (NCLNGenomicsReceiving@nih.gov)
Blood: George Duran (georgedu@stanford.edu)

5.8.3 RNAseq

5.8.3.1 Specimen(s) Receipt and Processing at the EET Biobank

FFPE tissue blocks will be sectioned to generate an initial hematoxylin and eosin (H&E)-stained slide. All H&E stained slides will undergo a pathology QA review and annotation for macrodissection. Following macrodissection, tumor tissue from unstained slides will be scraped for co-extraction of DNA and RNA. The nucleic acids will be analyzed to determine concentration and quality. RNA will be shipped to the central sequencing laboratory for analysis.

5.8.3.2 Site(s) Performing Correlative Study

See Section 5.8.2.2 for details.

5.8.3.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:

NCLN Genomics Laboratory at The University of Texas MD Anderson Cancer Center
Attn: Jincy Veliyathu or Khushali Rajendra Patel
Zayed Building
CTLU Z3.4020
6565 MD Anderson Blvd
Houston, TX 77030

5.8.3.4 Contact Information for Notification of Specimen Shipment

Thomas Forbes (NCLNGenomicsReceiving@nih.gov)

5.8.4 Phagocytosis Index

5.8.4.1 Specimen(s) Receipt and Processing at the EET Biobank

Blood will be collected in Green Top tubes at baseline and end of treatment or progression. Samples should be processed by Ficoll gradient purification to isolate PBMCs. PBMCs will be cryopreserved in cryovials and stored in liquid nitrogen vapor phase freezer.

5.8.4.2 Site(s) Performing Correlative Study

This assay will be performed by the Weinstock Laboratory at the Dana-Farber Cancer Institute

under the supervision of David Weinstock, M.D., and Salvia Jain, M.D.

5.8.4.3 Contact information for notification of specimen shipment

Weinstock Laboratory, Dana-Farber Cancer Institute
David Weinstock MD and Salvia Jain MD
Davidm_weinstock@dfci.harvard.edu
ssjain@bidmc.harvard.edu

5.8.5 Immunophenotyping of circulating tumor cells

5.8.5.1 Specimen(s) Receipt and Processing at the EET Biobank

Blood will be collected in Green Top tubes at baseline and end of treatment or progression. Samples should be processed by Ficoll gradient purification to isolate PBMCs. PBMCs will be cryopreserved in cryovials and stored in liquid nitrogen vapor phase freezer.

5.8.5.2 Site(s) Performing Correlative Study

This assay will be performed by the Khodadoust Laboratory and Stanford HIMC under the supervision of Michael Khodadoust, MD., Ph.D.

5.8.5.3 Contact information for notification of specimen shipment

Khodadoust Laboratory and Stanford HIMC
Michael Khodadoust MD PhD
mkhodado@stanford.edu
George Duran
georgedu@stanford.edu

5.8.6 T cell receptor sequencing

5.8.6.1 Specimen(s) Receipt and Processing at the EET Biobank

Blood will be collected in Green Top tubes at baseline, Cycle 1 Week 2, Cycle 3 Week 3, Cycle 6 Week1, and end of treatment or progression. Samples should be processed by Ficoll gradient purification to isolate PBMCs. PBMCs will be cryopreserved in cryovials and stored in liquid nitrogen vapor phase freezer.

5.8.6.2 Site(s) Performing Correlative Study

This assay will be performed at Adaptive Biotechnologies.

5.8.6.3 Contact information for notification of specimen shipment

Adaptive Biotechnologies.

5.8.7 Anti-drug antibody detection

5.8.7.1 Specimen(s) Receipt and Processing at the EET Biobank

Serum will be collected and aliquoted into cryovials by participating sites at baseline, Cycle 1 Week 2, Cycle 3 Week 3, Cycle 6 Week1, and end of treatment or progression. Frozen cryovials will be shipped to the EET Biobank and then stored in a -80°C freezer until shipping to Gilead Sciences for analysis.

5.8.7.2 Site(s) Performing Correlative Study

This assay will be performed at Gilead Sciences.

5.8.7.3 Contact information for notification of specimen shipment

Gilead Sciences.

6. TREATMENT PLAN

Hu5F9-G4 (magrolimab) binds to red blood cells and leads to erythrophagocytosis. During the screening period prior to initiation of Hu5F9-G4 (magrolimab) therapy, blood cell ABO phenotyping for minor antigens, type and screen (ABO/Rh), and Direct Antiglobulin Test (DAT) should be performed for each patient. This will facilitate allocation of properly cross-matched blood, should a blood transfusion be warranted (see Section 7.1.3).

6.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Hu5F9-G4 (magrolimab) dose will be calculated using the actual body weight of the patient at enrollment, and the dose may remain constant throughout the study unless a greater than 10% change in weight is observed.

All study patients will start **Hu5F9-G4 (magrolimab)** priming dose at 1 mg/kg IV followed by 30 mg/kg IV once a week in the first 2 cycles on a 28-day cycle. In cycle 3 and subsequent cycles, study patients will receive 30 mg/kg IV every 2 weeks on a 28-day cycle (see Table 2 below).

Hu5F9-G4 (magrolimab) may interfere with the assessment of RBC phenotyping. Hu5F9-G4 (magrolimab) binds to CD47 on RBCs and can mask detection of antibodies to minor antigens to the patient’s RBC and ABO/Rh phenotype, DAT and Ab screen.

Before Starting Hu5F9-G4 (magrolimab),

- The following assessments must be performed and resulted.
    - ABO/Rh type and screen,
    - Antibody Screen,
    - DAT
    - Extended RBC phenotyping including minor antigens such as CcDEe, Cw, MNSs, Kk, FyaFyb, and Jka Jkb
    - RBC genotyping 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). This may be performed for all patients in lieu of an extended RBC phenotyping.
- Ensure that the patient is provided a Patient Information Card containing their pre-study blood typing.

Hemoglobin must be ≥9.0 g/dL within 24 hours prior to the first 2 doses of Hu5F9-G4 (magrolimab) infusion. If several hemoglobin tests are performed prior to Dose 1 and Dose 2, the closest to the infusion should be considered. RBC transfusions are allowed to meet the minimum hemoglobin requirement prior to the first 2 doses.

Please refer to Section 7.1.4 for instructions for monitoring for anemia and anemia symptoms post-infusion.

Table 2: Dose De-escalation Schedule for Phase 1b

Dose De-escalation Schedule				
Dose Level	**Premedications: Precautions**	**Dose**		**Cycle Length**
		Hu5F9-G4 (Magrolimab)	**Mogamulizumab**	
Level 1 (starting dose level)	650-1,000 mg acetaminophen oral (PO) and 25 mg diphenhydramine (PO or IV) or a comparable regimen at least 15 minutes before the first two doses of Hu5F9-G4	1 mg/kg IV priming dose; Then 30 mg/kg IV weekly in Cycles 1 & 2 followed by Q2W ≥ Cycle 3). Give before mogamulizumab.	1 mg/kg IV (weekly for cycle 1, then Q2W starting from cycle 2)	28 Days
Level -1	Same as level 1	1 mg/kg IV priming dose; Then 20 mg/kg IV weekly in Cycles 1 & 2, followed byQ2W ≥ Cycle 3). Give before mogamulizumab.	1 mg/kg IV (weekly for cycle 1, then Q2W starting from cycle 2)	28 Days
Q2W = Every 2 weeks, IV = Intravenous **Priming dose will be given one week before Cycle 1 over 3 hours (+/- 30 minutes)* ***Hu5F9-G4 (magrolimab) to be administered before mogamulizumab on days when both treatments are given* ****** Within 24 hours prior to each of the first 2 doses of Hu5F9-G4infusion, patients must have a documented hemoglobin level of ≥9 g/dL. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet the minimum hemoglobin threshold prior to administering each of the first 2 doses of Hu5F9-G4. An additional hemoglobin must be checked 3 to 6 hours after the initiation of the first and second doses of Hu5F9-G4. 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.***				

As of the July 2023 amendment, the phase 1b portion has been completed with an enrollment of 6 patients at dose level 1. Out of the 6 patients treated, 1 experienced a DLT. The recommended phase 2 dose (RP2D) has been established as dose level 1 (30mg/kg magrolimab starting cycle 1).

Table 3: Regimen Description for Phase 2 (Hu5F9-G4 (magrolimab) + Mogamulizumab Arm)

Regimen Description					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Hu5F9-G4 (Magrolimab)	650-1,000 mg acetaminophen oral (PO) and 25 mg diphenhydramine (PO or IV) or a comparable regimen at least 15 minutes before the first two doses of Hu5F9-G4 (magrolimab).	1 mg/kg priming dose, then 30mg /kg per schedule	IV over 2 hours* and given before mogamulizumab **	1 mg/kg priming dose, then 30 mg/kg weekly for cycles 1-2, then Q2W starting from cycle 3	28 days (4 weeks)
Mogamulizumab	No additional premedications	1 mg/kg	IV	Weekly for cycle 1, then Q2W starting from cycle 2	
Q2W = Every 2 weeks, IV = Intravenous **Priming dose will be given over 3 hours (+/- 30 minutes)* ***Hu5F9-G4 (magrolimab) to be administered before mogamulizumab on days when both treatments are given* ****** Within 24 hours prior to each of the first 2 doses of Hu5F9-G4infusion, patients must have a documented hemoglobin level of ≥9 g/dL. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet the minimum hemoglobin threshold prior to administering each of the first 2 doses of Hu5F9-G4. An additional hemoglobin must be checked 3 to 6 hours after the initiation of the first and second doses of Hu5F9-G4. 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.***					

Table 4: Regimen Description for Phase 2 (Mogamulizumab Only Arm)

Regimen Description					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Mogamulizumab	650-1,000 mg acetaminophen oral (PO) and 25 mg diphenhydramine	1 mg/kg	IV	Weekly for cycle 1, then Q2W starting from cycle 2	28 days (4 weeks)

	(PO or IV) or a comparable regimen at least 15 minutes before the first dose of mogamulizumab.				
Q2W = Every 2 weeks, IV = Intravenous					

For patients who crossover to the Hu5F9-G4 (magrolimab)/mogamulizumab combination due to progression or lack of response after 6 months, no washout will be required and treatment will proceed with an identical schedule as the combination arm starting with the priming dose of Hu5F9-G4 (magrolimab).

6.1.1 CTEP IND Agent

6.1.1.1 Hu5F9-G4 (magrolimab)

All cohorts in both phase 1B and phase 2 portion will follow the same dosing schedule, though the dose of Hu5F9-G4 (magrolimab) may vary, following the de-escalation design of the phase 1B portion (see Table 2). For patients receiving the combination of Hu5F9-G4 (magrolimab) and mogamulizumab, treatment will start with a priming dose of Hu5F9-G4 (magrolimab) of 1mg/kg IV without mogamulizumab. Starting one week later, patients will receive the designated dose of Hu5F9-G4 (magrolimab) (either 30mg/kg or 20mg/kg IV) every week for eight weeks. After the first 8 weeks, the schedule of Hu5F9-G4 will change to every 2 weeks ongoing. Mogamulizumab treatment will also start one week after the priming dose of Hu5F9-G4 (magrolimab) at the FDA-approved dose and schedule.

6.1.2 Other Agent

6.1.2.1 Mogamulizumab

All cohorts in both phase 1B and phase 2 portion will follow the same dosing schedule. For patients receiving the combination of Hu5F9-G4 (magrolimab) and mogamulizumab, treatment will start with a priming dose of Hu5F9-G4 (magrolimab) of 1mg/kg IV without mogamulizumab. Mogamulizumab treatment will start one week after the priming dose of Hu5F9-G4 (magrolimab) at the FDA-approved dose and schedule of 1mg/kg IV every week for 4 weeks. After the first 4 weeks of weekly mogamulizumab, the mogamulizumab schedule will change to every 2 weeks ongoing.

6.2 Definition of Dose-Limiting Toxicity

DLT Definition: A DLT is defined as any Grade 3 or greater AE that is assessed as related to at least 1 study treatment that occurs during the DLT Assessment Period (DLT exceptions are defined below). The DLT period during the phase 1 study will be 4 weeks from the first infusion of Hu5F9-G4 (magrolimab) (priming infusion). To be assessable for a DLT, patients must have

received at least three infusions of Hu5F9-G4 (magrolimab), two infusions of mogamulizumab, and completed four weeks of assessment, or else have experienced a DLT anytime after receiving the priming dose of Hu5F9-G4 (magrolimab). Patients unable to receive the planned treatment during the four weeks due to treatment-related adverse events will also be considered to have experienced a DLT.

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

- Grade 3 anemia; however, Grade 3 hemolytic anemia is considered a DLT.
- Grade 3 hyperbilirubinemia 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, acute pain, or skin toxicity that resolves to ≤Grade 2 within ≤72 hours after medical management (*e.g.*, supportive care, including immunosuppressant treatment) has been initiated.
- Grade 3 fatigue that resolves to ≤Grade 2 within 1 week on study.
- Grade 3 magrolimab-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 electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia, *etc*.) that resolves to ≤Grade 2 or baseline within 1 week.
- Grade 3 or 4 lymphopenia or grade 3 leukopenia not associated with other clinically significant consequences.
- Transient (≤48 hours) Grade 3 fatigue, local reactions, flu-like symptoms, fever, headache, nausea, emesis, and diarrhea.
- Other single laboratory values out of normal range that have no clinical correlate, and resolve to Grade ≤1 or to baseline within 7 days with adequate medical management.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- Grade 3 rash, erythroderma, skin pain or photosensitivity that resolves to ≤Grade 2 within 1 week with adequate medical management. Grade 4 rash or any grade Stevens-Johnson syndrome or toxic epidermal necrolysis will be considered DLTs.

Management and dose modifications associated with the above adverse events are outlined in Section 7.

Dose de-escalation will proceed within each cohort according to the following scheme (Figure 7) (Hong *et al*., 2019). Dose-limiting toxicity (DLT) is defined above.

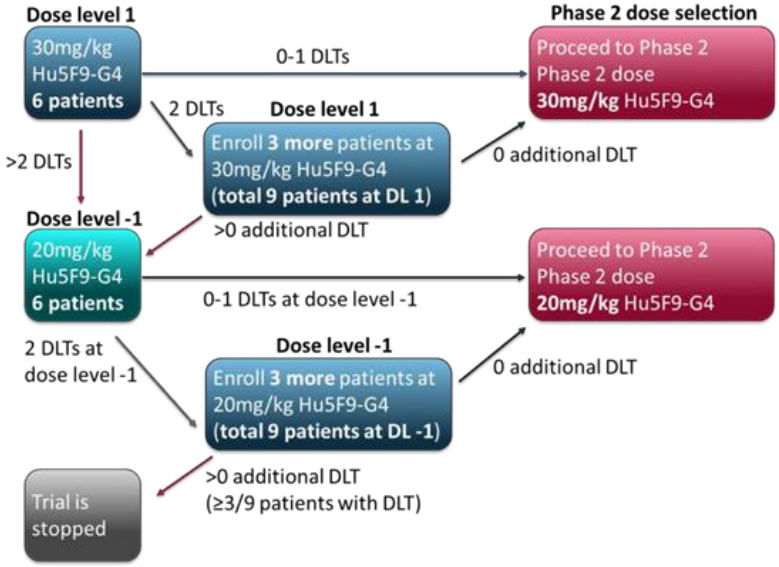


Figure 7: Phase 1b Dose De-escalation Design

Six patients will be enrolled at dose level 1 of 30mg/kg Hu5F9-G4 (magrolimab) and 1mg/kg mogamulizumab. If ≤ 1 DLT is observed in the initial 6 patients, then dose level 1 will be selected as the RP2D. If 2 DLTs are observed in the initial 6 patients, then an additional group of 3 patients will be enrolled at dose level 1. If there are no DLTs in this 3 patient group, then dose level 1 will be selected as the RP2D. If at any point there are >2 DLTs seen at dose level 1, then this dose level will close, and 6 patients will be enrolled at the new dose level -1: 20mg/kg Hu5F9-G4 (magrolimab) and 1mg/kg mogamulizumab. If ≤ 1 DLT is observed in the initial 6 patients, then dose level -1 will be selected as the RP2D. If 2 DLTs are observed in the initial 6 patients, then an additional group of 3 patients will be enrolled at dose level -1. If at any point there are >2 DLTs seen at dose level -1, then the trial will be stopped for unacceptable toxicity. It is believed that further reductions below a dose of 20mg/kg would not achieve adequate target occupancy for Hu5F9-G4 (magrolimab).

6.3 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of Hu5F9-G4 (magrolimab) and mogamulizumab with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Corticosteroids may interfere with accurate disease response assessment. High potency topical corticosteroids and systemic corticosteroids doses greater than 10mg prednisone daily or its equivalent are prohibited unless needed to treat adverse events. Effort should be made to taper steroids to the minimum required dose. Other anti-lymphoma therapies are prohibited including retinoic acids and phototherapy. Appendix C (Patient Clinical Trial Wallet Card) should be provided to patients if available.

6.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 12 cycles or until one of the following criteria applies:

- Disease progression. Patients randomized to the mogamulizumab-only arm may crossover as per section 6.6. Relapse in skin or blood compartments as defined by the response criteria is not considered progression and does not require removal from the treatment protocol.
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

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

6.5 Duration of Follow-Up

Patients will be followed for two years after their last treatment, until progression, or until the start of the next significant treatment, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

6.6 Cross-over

6.6.1 Eligibility for cross-over:

Subjects randomized to the mogamulizumab-only arm will be eligible to cross-over to the combination arm of Hu5F9-G4 (magrolimab) and mogamulizumab if they meet EITHER of the following criteria:

1. Have received at least 2 full treatment cycles of mogamulizumab and meet global criteria for progression of disease

2. Have received at least 6 full treatment cycles of mogamulizumab and meet global criteria for stable disease

Additionally, to be eligible for cross-over, subjects must meet BOTH of the following criteria:

1. Meet the eligibility criteria at the time of cross-over. The only exception to the eligibility criteria will be that subjects who have active large cell transformation (LCT) at the time of cross-over will be eligible for cross-over.

2. Subjects must also have a skin biopsy performed within 4 weeks prior to cross-over with a pathologic diagnosis confirming cutaneous lymphoma. It is strongly recommended to perform molecular studies of TCR clonality if there is ambiguity in the diagnosis. This criteria is to exclude the possibility of progression incorrectly being attributed to a mogamulizumab-associated rash.

Subjects will have 4 weeks from the date of progression to meet eligibility for cross-over.

6.6.2 Procedures related to cross-over:
Subjects who cross-over to the combination therapy arm will adhere to the study calendar. The following procedures do not need to be repeated at baseline if performed within 4 weeks of cross-over:

- Imaging
- Flow cytometry
- Skin biopsies
- Correlative blood collection

7. DOSING DELAYS/DOSE MODIFICATIONS

Dose Level	Hu5F9-G4 (Magrolimab) Maintenance Dose	Mogamulizumab
-1	1 mg/kg IV priming dose; Then 20 mg/kg IV weekly in Cycles 1 & 2 followed by Q2W in ≥ Cycle 3. Give before mogamulizumab.	Weekly for cycle 1, then Q2W starting from cycle 2
1	1 mg/kg IV priming dose; Then 30 mg/kg IV weekly in Cycles 1 & 2	Weekly for cycle 1, then Q2W starting from cycle 2

	followed by Q2W in ≥ Cycle 3. Give before mogamulizumab.	

Dose reductions are not required for Hu5F9-G4 (magrolimab), except in case of anemia. For all other treatment-related adverse events, Hu5F9-G4 (magrolimab) can be reduced by 1 dose level if a Grade 3 or higher AE that is related to Hu5F9-G4 (magrolimab) is observed and does not resolve within 2 weeks.

The following modifications should be performed for treatment-related adverse events.

Nausea	**Management/Next Dose for Hu5F9-G4 (magrolimab) and Mogamulizumab**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	
Recommended management: antiemetics.	

Vomiting	**Management/Next Dose for Hu5F9-G4 (magrolimab) and Mogamulizumab**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	
Recommended management: antiemetics.	

Diarrhea	**Management/Next Dose for Hu5F9-G4 (magrolimab) and Mogamulizumab**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.	

Neutropenia	**Management/Next Dose for Hu5F9-G4 (magrolimab) and Mogamulizumab**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	
Recommended management: Growth factor	

Thrombocytopenia	**Management/Next Dose for Hu5F9-G4 (magrolimab) and Mogamulizumab**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	

Anemia	**Management/Next Dose for Hu5F9-G4 (magrolimab)**	**Management/Next Dose for Mogamulizumab**
≤ Grade 1	No change in dose	No change in dose
≤ Grade 2	No change in dose	No change in dose
Grade 3 hemolytic anemia that is medically significant (requiring hospitalization or prolongation of existing hospitalization, disabling, or limiting self-care ADLs)	First occurrence: Reduce by 1 dose level. • If recurs after 1 dose level reduction: permanently discontinue unless patient is clinically benefitting. • Second occurrence: permanently discontinue	Hold* until ≤ Grade 2. Resume at same dose level.
Grade 4	First occurrence: permanently discontinue unless patient is clinically benefitting.**	First occurrence: permanently discontinue unless patient is clinically benefitting.**
*Patients requiring a delay of >2 weeks should go off protocol therapy. **If Grade 4 anemia is unrelated to underlying disease, permanently discontinue Hu5F9-G4 (magrolimab) regardless of clinical benefit. Mogamulizumab may be resumed if anemia is resolved to Grade ≤ 2 and if there may be a clinical benefit from the treatment.		
Recommended management: Transfusions as per section 7.1		

Rash* (including maculopapular, pruritus, erythroderma, photosensitivity, and skin pain)	**Management/Next Dose for Hu5F9-G4 (magrolimab)**	**Management/Next Dose for Mogamulizumab**
Grade 2	Magrolimab** should be continued without dose modification.	Mogamulizumab*** may be held at investigator's discretion.
Grade 3	Magrolimab** may be held at the investigator's discretion.	Mogamulizumab*** may be held at investigator's discretion.
Grade 4	Off protocol therapy	Off protocol therapy
*It is recommended to perform skin biopsies when possible with molecular T-cell receptor clonality studies to help distinguish rash from progressive disease ** Magrolimab may be held at the investigator's discretion for up to 2 weeks from the time of the scheduled infusion for grade 3 rash. Patients requiring a magrolimab delay of >2 weeks from their scheduled infusion should go off protocol therapy. Upon restarting magrolimab after a delay, there will be no dose reduction. *** Mogamulizumab may be held up to 4 weeks from the time of the scheduled infusion for grade 2-3 rash. Patients requiring a mogamulizumab delay of >4 weeks from their scheduled infusion should go off protocol therapy. Upon restarting mogamulizumab after a delay, there will be no dose reduction.		
Recommended management: High potency topical steroids may be used for grade 2-3. Subjects should apply topical steroids only to areas of suspected rash and avoid areas of known lymphoma disease and should try to reduce topical steroids to medium or low potency as tolerated. For grade 2, systemic corticosteroids may be given. For grade 3, systemic corticosteroids should be given. A dose of 40mg prednisone daily or equivalent is suggested. If systemic corticosteroids are given, efforts should be made to taper as tolerated to a dose of 10mg prednisone daily or equivalent.		

All Other Drug-related Toxicity***	**Management/Next Dose for Hu5F9-G4 (magrolimab) and Mogamulizumab**
Grade 3	Hold** until ≤ Grade 2.
Grade 4	Off protocol therapy
* Patients with intolerable or persistent Grade 2 drug-related AE may hold study medications for up to 2 weeks at physician discretion. **Patients requiring a delay of >2 weeks should go off protocol therapy. *** Lymphopenia and/or leukopenia are the pharmacologic effect of mogamulizumab and will not be considered an AE for this study. However, neutropenia will be considered an AE and managed as above.	

All Other Drug-related Toxicity* **	**Management/Next Dose for Hu5F9-G4 (magrolimab) and Mogamulizumab**

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 2 weeks of the interruption. The reason for interruption should be documented in the patient's study record.

7.1 Safety Management Guidelines

7.1.1 Management of Infusion-related Reactions

The most common adverse events associated with IRRs include chills, pyrexia, back pain, nausea, vomiting, hypotension, dyspnea, and headache. These primarily occur with the first two doses of Hu5F9-G4 (magrolimab) (1 mg/kg), and are mostly observed during the infusion or several hours afterward.

Preventive Measures

Premedication should include oral acetaminophen and an antihistamine (IV or oral) before the initial doses of Hu5F9-G4 (magrolimab) or in the case of re-priming of Hu5F9-G4 (magrolimab). Premedication is required prior to the administration of the intial doses of Hu5F9-G4 (magrolimab). Refer to Section 6.1 Agent Administration.

Management of IRRs

- For grade 1 IRRs, described as mild transient reaction, infusion interruption is not indicated, intervention is not indicated:
    - Remain at bedside and monitor patient until recovery from symptoms.
- For grade 2 IRRs, infusion interruption is indicated, but patient responds promptly to symptomatic treatment (*e.g.*, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, IV fluids); and prophylactic medications are indicated for ≤24 hours:
    - Stop the Hu5F9-G4 (magrolimab) infusion, begin an intravenous (IV) infusion of normal saline, and consider treating the patient with diphenhydramine 50 mg IV (or equivalent) and/or 500–750 mg oral acetaminophen.
    - Remain at bedside and monitor patient until resolution of symptoms.
    - Corticosteroid therapy may also be given at the discretion of the Investigator.
    - If the infusion is interrupted, wait until symptoms resolve, then restart the infusion at 50% of the original infusion rate.
    - If no further complications occur after 1 hour (± 10 minutes), the rate may be increased to 100% of the original infusion rate. Monitor the patient closely.
    - If symptoms recur, stop infusion and disconnect patient from the infusion apparatus. No further Hu5F9-G4 (magrolimab) will be administered at that visit.

- Premedications should be considered before any future infusions.
- The amount of Hu5F9-G4 (magrolimab) infused must be recorded on the case report form (eCRF).
- Patients who experience a grade 2 IRR during the post-infusion observation period that does not resolve during that time should be observed until the AE resolves, with vital sign measurements as medically indicated for the management of the AE.

- For grade 3 or grade 4 IRR, where grade 3 is described as prolonged infusion-related reactions (*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 indicated.
    - Immediately discontinue infusion of Hu5F9-G4 (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 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 have grade 4 IRRs occurring with the first dose (priming dose) will be permanently discontinued from study treatment.
    - Patients who experience grade 3 IRRs must be given premedication prior to all subsequent doses. In this setting, premedication with oral acetaminophen (650 mg), oral or IV diphenhydramine (25–50 mg), and IV dexamethasone (4–20 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 with a corticosteroid and still experience a grade 3 or 4 infusion-related reaction will be permanently discontinued from study treatment.
    - Investigators should follow their institutional guidelines for the treatment of anaphylaxis.
    - All patients with grade 3 or greater IRRs will be observed until the AE(s) resolves or stabilizes, with vital sign measurements and additional evaluations, as medically indicated for the management of the AE(s).

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

A premedication regimen (oral acetaminophen and diphenhydramine, or comparable regimen) is required before the initial doses of Hu5F9-G4 (magrolimab) and in case of repriming of the participant after >4 weeks interruption in Hu5F9-G4 (magrolimab) treatment.

7.1.2 Tumor Lysis Syndrome

In the case of evidence for tumor lysis syndrome associated with Hu5F9-G4 (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.

7.1.3 Hemagglutination and Microangiopathy

In the phase 1 trial experience with Hu5F9-G4 (magrolimab) in solid tumors and AML, agglutination of RBCs has been observed on peripheral smear. Hu5F9-G4-related microangiopathy is a possible sequela of hemagglutination; however, it has not been observed in the ongoing phase 1 clinical trials to date. In addition, AEs may be associated with findings of hemagglutination. Monitoring of hemagglutination and microangiopathy includes physical exam assessments, complete blood counts (CBCs), peripheral smears, serum chemistries, and D-dimer testing as outlined in the schedule of assessments (SOA). Peripheral smears will be read by local sites with reporting of RBC agglutination, spherocytosis, and evidence of RBC destruction (*e.g.*, schistocytosis, fragments) when present. The presence or absence of hemagglutination and/or microangiopathy on peripheral smear will be incorporated into the AE severity grading for hemagglutination and microangiopathy, as described below. The degree of peripheral smear findings will be quantified according to the appropriate scale (Appendix H) for sites that have the capability to do so, but is not required. Peripheral smear slides will be retained by the Sponsor and stored for future analyses. AEs relating to hemaggplutination and microangiopathy will be graded for toxicity according to the scale below.

AE Severity Grading for Hemagglutination and Microangiopathy

Grade 1: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that is asymptomatic or mild, not requiring intervention

Grade 2: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that requires medical intervention

Grade 3: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that is medically significant, requiring hospitalization or prolongation of existing hospitalization, disabling, or limiting self-care activities of daily living (ADLs)

Grade 4: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that is life threatening or requires urgent intervention

Grade 5: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that results in death

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

Patients must have a documented hemoglobin ≥9 g/dL within 24 hours prior to receiving the first and second dose of Hu5F9-G4 (magrolimab). Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet the minimum hemoglobin threshold prior to administering the first two doses of magrolimab. An additional hemoglobin measurement must be performed 3 to 6 hours after the initiation of the first and second doses of Hu5F9-G4 (magrolimab). 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.

Patients with a low baseline hemogloblin level, especially those with cardiac history or risk factors, must be monitored closely after initial administrations of Hu5F9-G4 (magrolimab) as preexisting anemia can be exacerbated.

Hu5F9-G4 (magrolimab) binds to red cells and leads to erythrophagocytosis. This, coupled with anemia from other causes in patients with cancers, means that care has to be taken with RBC cross-matching and packed red blood cell (PRBC) transfusions. There is a possibility that treatment with Hu5F9-G4 (magrolimab) may obscure assessment of RBC phenotyping.

During the Screening Period prior to initiation of Hu5F9-G4 (magrolimab) therapy, blood cell ABO phenotyping for minor antigens, type and screen (ABO/Rh), and Direct Antiglobulin Test (DAT) will be performed for each patient. This, together with using the prior phenotype, will facilitate allocation of properly cross-matched blood, should a blood transfusion be warranted.

Procedure for patients after exposure to Hu5F9-G4 (magrolimab):

1. ABO, Rh, and DAT may be pan-reactive due to Hu5F9-G4 (magrolimab) binding to red cells. Therefore, if a non-urgent transfusion is ordered by the Investigator, perform the following procedures:
    - Front Type: ethylenediaminetetraacetic acid (EDTA)/glycine-acid (EGA) Treat cells ×2 (maximum) and Warm Wash ×4 (minimum) with 0.9% Saline.
    - Back Type: Perform reverse anti-human globulin for both A and B.
    - If a valid ABO type cannot be obtained, mark the final report as invalid and notify the transfusion service for the site.
2. Antibody screen
   If a pan-agglutinin/warm autoantibody is present in low ionic strength solution (LISS), repeat the antibody screen with polyethylene glycol (PeG). Perform PeG adsorption studies and elution studies.
3. Notify blood transfusion centers/blood banks of this interference with blood bank testing and inform them that a patient will receive Hu5F9-G4 (magrolimab).
4. For all elective RBC and platelet transfusions, use leukocyte-reduced and gamma-irradiated units per institutional guidelines.
5. For RBC transfusions, phenotype/genotype matched units are preferred.
6. In case ABO/Rh type cannot be resolved, use pretreatment (historical) phenotype/genotype matched units for minor RBC antigens (CcDEe and Kk, to the feasible extent). Regarding the ABO type, historical blood group or O type can be used as per the institutional guidelines.

7. For emergency transfusions, the transfusion centers may consider using emergency Group O red cells if phenotype/genotype matched units are not available.
8. Cross-match interference by RBCs due to treatment with Hu5F9-G4 (magrolimab) may be resolved by use of gamma-clone anti-IgG and multiple alloadsorptions with papain-treated RBC samples, pooled single donor apheresis platelets or commercial human platelet concentrate product if required

7.1.5 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 any of the blood groups M, N, and S compromising the MNS system [MNS]), 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 Coomb's crossmatch-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. Such instances will be documented, along with consent signatures obtained from ordering physicians, according to best practices in blood bank policies and procedures.

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.

7.1.6 Thromboembolic Events

Thromboembolic events including deep vein thromboses and pulmonary embolisms, have been reported in some patients receiving Hu5F9-G4 (magrolimab), sometimes early in therapy.

- No clear or consistent relationship between clinical and thromboembolic events and Hu5F9-G4 (magrolimab) use has been observed.
- Close monitoring for symptoms of thromboembolic events is required.
- Patients should be treated as per standard of care.

7.1.7 Pneumonitis

Pneumonitis has been infrequently observed in patients receiving Hu5F9-G4 (magrolimab). It is currently unknown if Hu5F9-G4 (magrolimab)increases the risk of pneumonitis.

In instances of suspected pneumonitis:

- First, rule out non-inflammatory causes (*e.g.*, infections).

- If non-inflammatory cause identified, treat accordingly and continue therapy per protocol.
- Evaluate with imaging (*e.g.*, chest x-ray or computed tomography) and pulmonary consultation.
- Management of potential pneumonitis and follow-up management of Immune-Related Adverse Events Treated with Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline should be followed.

Pneumonitis Management Algorithm

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

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

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 10.1.

8.1 CTEP IND Agent

8.1.1 Hu5F9-G4 (magrolimab) (NSC 809249)

Classification*:* A monoclonal antibody CD47 inhibitor

CAS Registry Number*:* 1682749-68-3

Molecular Formula: $C_{6462}H_{9960}N_{1718}O_{2027}S_{48}$ **M.W.:** 145687.6 Daltons (predicted)

Mode of Action*:* Phagocytosis of tumor cells is blocked when CD47, a cell surface glycoprotein widely expressed by cancer cells, binds to the receptor, SIRPα, found on innate immune system cells like macrophages and dendritic cells. Hu5F9-G4 blocks the binding of this "don't eat me" signal which then allows the activation of macrophages to phagocytose cancer cells through the induction of pro-phagocytic signaling. Nonclinical studies show that CD47 inhibition combined with other anti-tumor antibodies like rituximab or cetuximab has the potential to provide synergistic pro-phagocytic signaling to macrophages.

Description: Hu5F9-G4(magrolimab) is a recombinant humanized IgG4 monoclonal antibody of the IgG4 kappa isotype containing a Ser-Pro substitution in the hinge region of the heavy chain. It comprises a disulfide linked glycosylated tetramer, consisting of 2 identical 444 amino acid heavy gamma chains and 2 identical 219 amino acid kappa light chains.

How Supplied: Gilead Sciences supplies and CTEP, DCTD, NCI distributes Hu5F9-G4 (magrolimab) injection as 200 mg/10 mL (20 mg/mL) single-use vials in a type I borosilicate glass vial with coated elastomeric stopper and aluminum crimp over seals with a flip-off cap. Hu5F9-G4(magrolimab) is a sterile, clear to slightly opalescent, colorless to slightly yellow, preservative-free liquid in 10 mL vials. The product is formulated in 0.01% (weight/volume [w/v]) polysorbate 20, 5% (w/v) sorbitol, 10 mM sodium acetate / acetic acid, pH 5.0, and sterile water for injection.

Preparation: Use pre-filled 250 mL and 500 mL normal saline bag (preferred) but an empty IV bag is also acceptable.

Magrolimab is compatible in IV bags and peripheral/central IV line made of the following materials: Polyvinyl chloride (PVC) with or without DEHP; Polyolefin (PO), Polyethylene (PE) and Polypropylene (PP); Ethyl vinyl acetate (EVA), Polyether sulfone (PES) in-line filters; Polyurethane (PU); Fluorinated ethylene propylene (FEP); Thermoplastic elastomer (TPE); Stainless steel; Silicone; Polycarbonate (PC); Acrylonitrile butadiene styrene (ABS); Polytetrafluoroethylene (PTFE); Low density polyethylene (LDPE); Polyimide; Delrin; Acrylate polymer; Polyoxymethylene; Polyamide ; Titanium; Methyl methacrylate acrylonitrile butadiene styrene (MABS); Acrylic copolymer and nylon; Polyvinylchloride (PVC) with Tris (2-ethylhexyl) Trimellitate (TOTM); Polyester or copolyester ; Polyvinylidene fluoride ; Ethyl acrylate-styrene-methyl methacrylate copolymer; Isoprene rubber or polyisoprene; Fluorosilicone; and Polyethylene terephthalate

The following proprietary closed system transfer devices (CSTDs) are compatible with magrolimab: PhaSeal, PhaSeal Optima, Equashield, ChemolockT, SmartSite with Texium and Spiros.

Magrolimab IV solution can be prepared from multiple lots but using one lot per dose is preferred.

- For doses of 1 mg/kg or less, dilute dose in 250 mL 0.9% sodium chloride
- For doses greater than 1 mg/kg, dilute dose in 500 mL 0.9% sodium chloride

- Obtain the required number of vials and examine them for discoloration, cloudiness, or particles. Do not use if particulate matter or discoloration is noted.
- If using a **pre-filled 250 mL or 500 mL 0.9% sodium chloride bag**, remove normal saline volume equivalent to the calculated dose volume of magrolimab from the pre-filled saline bag. Then, add the calculated dose volume of magrolimab into the pre-filled saline IV bag.
- If using **an empty IV bag**, add the calculated volume of 0.9% sodium chloride into the empty IV bag followed by the calculated dose volume of magrolimab to make a total volume of 250 mL or 500 mL.
- Gently invert the IV bag 3-6 times to mix the solution. Avoid foaming IV solution. If particulate matter or discoloration occurs, do not use the IV preparation.

The prepared IV solution can be stored as follows:

- 25^0 C (77^0 F) up to 8 hours, which includes the preparation time and the completion time of the infusion. Discard if exceeding 8 hours.
- 2°C - 8°C (36° F to 46° F) for up to 16 hours, which includes the preparation time and the completion time of the infusion including 1 hour for IV solution to equilibrate at room temperature before administration. Discard IV if exceeding 16 hours.

Storage: Store vials at 2°C - 8°C (36° F to 46° F) in the original carton, protected from light. Do not freeze.

If a storage temperature excursion is identified, promptly return Hu5F9-G4 (magrolimab) to 2°C -8°C (36° F to 46° F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Shelf-life stability studies of the intact or unused vials are on-going.

CAUTION: The single-use injectable vial contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded 8 hours after initial entry.

Route of Administration: Intravenous. Do not administer as an IV bolus.

Method of Administration: A priming dose of Hu5F9-G4 (magrolimab) is required 1 week prior to Cycle1 Day1. The priming dose (1 mg / kg) will be infused over 3 hours (+/- 30 minutes) via a

peripheral or central line through a polyethersulfone (PES) in-line IV filter set. Prime the IV line with the prepared IV solution before starting the infusion. After completing the infusion, the IV line can be flushed with 40 mL normal saline at the same infusion rate in the table below or as per institutional guidelines. Subsequent IV doses are to be infused over 2 hours (+/- 10 minutes)**.**

Dose	Infusion volume (mL)	Infusion time	Rate (mL/min)	Rate (mL/Hour)
1 mg/Kg	250	3 hours (+/- 30 mins)	1.4	83
15 mg/Kg	500	3 hours (+/- 30 mins)	2.8	167
30 mg/Kg	500	2 hours (+/- 30 mins)	4.2	250

Oral acetaminophen 650 mg to 1000 mg and oral/IV diphenhydramine 25 to 50 mg or comparable regimen are acceptable premedication. Premedication is required prior to the administration of the first 4 doses of magrolimab and in case of reintroduction with repriming. Premedication during subsequent infusions may be continued based on the treating investigator's clinical judgment and the presence/severity of prior infusion-related reactions. In the case of a Grade 3 infusion-related reaction, a premedication regimen for subsequent infusions may be needed. Refer to the protocol for additional guidance.

Patient Care Implications: Advise men and women of reproductive potential to use effective contraception while receiving study treatment and for 4 months after the last dose of Hu-5F9 (magrolimab). Male patients whose partners are pregnant may continue study treatment and should use barrier method contraception (condom) to prevent exposing the fetus. Refer to the protocol document for specific guidance.

Since infusion reactions can occur, all patients should be monitored for 1-hour post-infusion for the priming dose. Patients who experience any treatment-related adverse events during the observation period should be further monitored as clinically appropriate (e.g., for up to 24 hours post-dose). All patients should be monitored for 1-hour post-infusion for Cycle 1. Further doses (Cycle 2+) do not require post-infusion observation. Patients who experience any treatment-related AEs during the observation period should be further monitored as clinically appropriate. Follow the protocol's instructions for managing infusion symptoms and hypersensitivity to Hu5F9-G4 (magrolimab).

Availability

Hu5F9-G4 (magrolimab) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Hu5F9-G4 (magrolimab) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.5).

8.1.2 Agent Ordering and Agent Accountability

8.1.2.1 NCI-supplied agents may be requested by eligible participating Investigators (or their

authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Confirmation of study patient enrollment onto the study is required for initial drug shipment.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.2.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.3 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov

- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

8.2 Commercial Agent(s)

8.2.1 Mogamulizumab (NSC 791064)

Please refer to the Mogamulizumab Package Insert for complete information.

Other Names: KW-0761, AMG 761, POTELIGEO®

Classification: Anti-CC chemokine receptor 4 (CCR4) MAb

Molecular Weight: ~149 kDa

Mode of Action: Mogamulizumab selectively binds to and blocks the activity of CC chemokine receptor 4 (CCR4), a G-coupled-protein receptor for C-C chemokines expressed on the surfaces of some types of T cells, endothelial cells, and neurons. Mogamulizumab is a defucosylated, humanized, IgG1 MAb with lack of fucose resulting in enhanced antibody-dependent cellular cytotoxicity (ADATA COORDINATING CENTER) activity. It may induce ADATA COORDINATING CENTER against CCR4-positive T cells and inhibit CCR4-mediated signal transduction pathways leading to chemokine-mediated cellular migration and proliferation of T cells, and chemokine-mediated angiogenesis.

How Supplied: Mogamulizumab (mogamulizumab-kpkc) injection is a sterile, preservative-free, clear to slightly opalescent colorless solution supplied in a carton containing one 20 mg/5 mL (4 mg/mL), single dose glass vial (NDC 42747-761-01).
Preparation: Visually inspect drug product solution for particulate matter and discoloration prior to administration. Mogamulizumab is a clear to slightly opalescent colorless solution. Discard the vial if cloudiness, discoloration, or particulates are observed.

- Calculate the dose (mg/kg) and number of vials of Mogamulizumab needed to prepare the infusion solution based on patient weight.
- Aseptically withdraw the required volume of Mogamulizumab into the syringe and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP. The final concentration of the diluted solution should be between 0.1 mg/mL to 3.0 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard any unused portion left in the vial.

The diluted solution is compatible with polyvinyl chloride (PVC) or polyolefin (PO) infusion bags.

Storage: Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original package to protect from light until time of use. Do not freeze. Do not shake.

Stability: After preparation, infuse the Mogamulizumab solution immediately, or store under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 4 hours from the time of infusion preparation. Do not freeze. Do not shake.
Route of Administration: Intravenous (IV) infusion

Method of Administration:

- Administer infusion solution over at least 60 minutes through an intravenous line containing a sterile, low protein binding, 0.22 micron (or equivalent) in-line filter.
- Do not mix Mogamulizumab with other drugs.
- Do not co-administer other drugs through the same intravenous line.

Patient Care Implications: Refer to the protocol for information on evaluation and management of infusion related reactions.

Agent Ordering: Commercially available from various manufacturers. See package insert for further information.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

This is a combined phase 1b/2 multicenter, open label, interventional study to evaluate the safety (phase 1b) and efficacy (phase 2) of the combination of Hu5F9-G4 (magrolimab) with mogamulizumab. The phase 1b portion will be a single arm, dose de-escalation 6+3 design to determine a RP2D of Hu5F9-G4 (magrolimab), and will enroll 6-18 patients. A formal amendment is required to proceed to the phase 2 portion of the protocol. The phase 2 portion will be an open label, randomized, two-arm design with for patients with relapsed/refractory MF or SS, randomized 1:1 to either mogamulizumab alone or mogamulizumab plus Hu5F9- G4 (magrolimab), and will enroll 82 patients.

The primary endpoint for the randomized phase 2 portion will be ORR6 – a composite endpoint of both response rate and duration of response. As a historical reference, the ORR6 of the intention-to-treat analysis of mogamulizumab arm of the MAVORIC trial was 21%.

Phase 1b Design Operating Characteristics: The phase 1b 6+3 clinical trial design has the following operating characteristics.

	No Dose	L1	L2	Months to Complete (mean, median, range)	Number of evaluable patients treated (mean, median, range)
True DLT Probability	**-**	**0.1**	**0.15**	**-**	
Prob MTD 3+3	0.03	0.22	0.75	8.4, 7.6 (3.3-22.1)	6.6, 6 (4-12)
Prob MTD 6+3	0.01	0.13	0.86	6.5, 5.6 (2.0-25.1)	6.9, 6 (5-18)
True DLT Probability	**-**	**0.1**	**0.3**		
Prob MTD 3+3	0.08	0.53	0.39	9.9, 9.5 (3.5-26.2)	8.0,8.0 (4-12)

Prob MTD 6+3	0.03	0.49	0.48	8.6, 8.1 (2.0-25.3)	9.4,9.0 (5-18)
True DLT Probability	**-**	**0.2**	**0.4**		
Prob MTD 3+3	0.32	0.49	0.19	10.2, 9.8 (3.2-26.2)	8.4,8.0 (4-12)
Prob MTD 6+3	0.20	0.55	0.25	9.7, 9.2 (2.1-24.2)	10.8,11.0 (5-18)
True DLT Probability	**-**	**0.3**	**0.5**		
Prob MTD 3+3	0.59	0.33	0.08	9.5, 9.2 (2.5-23.2)	8.0,8.0 (4-12)
Prob MTD 6+3	0.47	0.42	0.10	9.9, 9.5 (2.2-24.3)	11.3, 11 (5-18)

These estimates are based on 800 simulations, and assume a 30% screen failure, and a 20% inevaluable rate (see oneq.netlify.app for simulation engine). The study starts on dose level 2 and only de-escalates if required based on the rules (2 DLTs in the traditional 3+3 design, and 3 DLTs in the 6+3 design). The simulations assume a 10 day mean interarrival time. As the 6+3 design does not de-escalate with 2 DLTs out of 6 patients, it tolerates slightly more toxicity than the traditional 3+3 design. Specifically, a maximum of 2 out of 9 patients with a DLT (or 22.2%) observed toxicity at the MTD is accepted rather than a maximum of 1 out of 6 with a DLT (16.7%) with 3+3 design. These operating characteristics are such that with a 15% DLT rate at the starting dose, the MTD will be selected as that dose with 86% probability, and with a 50% DLT rate at the starting dose, the MTD will be less than that dose with 90% probability. The rules of the 6+3 determine the maximum tolerated dose, but the RP2D may be the MTD or less depending on the severity of the DLTs, sub-DLT level toxicities, later toxicities and clinical judgement. In the phase 2 randomized study, further interim safety analyses are conducted to make sure the observed DLT rate does not exceed 30%.

Phase 2 Power and Sample Size: We anticipate a lower ORR6 response rate for the control mogamulizumab arm of this trial to be lower than that for MAVORIC (Kim *et al*, 2018). This is because mogamulizumab is now FDA-approved and is increasingly being utilizing in the treatment of patients with SS in particular, where higher response rates were seen in the MAVORIC trial. Therefore, we anticipate that referrals to this trial will be more skewed towards MF than MAVORIC where Sezary patients comprised 45% of the intention-to-treat (ITT) population. We have therefore estimated that the control arm of this cohort will have an ORR6 of 16% for the purposes of the power calculation, with 30% ORR6 in the SS patients and 10% in the MF patients, who we estimate will comprise 70% of the trial (resulting in a combined ORR6 of 16%). With 82 patients (41 in each arm), and assuming the 2 strata with SS have an ORR6 of 30% and the 2 strata with MF have an ORR6 of 10%, and looking to detect an odds ratio of 3.2 associated with the addition of Hu5F9-G4 (magrolimab), there is 86% power to detect this effect size with 41 patients in each treatment arm, with a type I error (one-sided) of 0.15. The choice of the type I error is based on (Rubinstein *et al*., 2005). This odds ratio is associated with detecting an improvement from 16% to 36% in the ORR6. This calculation is based on the Mantel-Haenszel (Cochran) test for 2x2 tables for 4 strata (based on MF vs SS and Stage) and calculated with nQuery+nTerim 4.0 (2015).

In addition, if the Sezary patients are more prevalent than we anticipate, reaching a percentage of

patients reflected in the MAVORIC trial (45%), the combined ORR6 is 19% and the power increases from 86% to 88%.

Interim Futility Analysis: A planned interim futility analysis will be performed as per the Wieand rule. When 50% of the patients are evaluable, if the ORR6 of the combination is not superior to the single agent, accrual will hold.

Interim Safety Analysis: Before proceeding to the Phase 2 study, the Phase 1b will report satisfaction of the DLT safety criteria and provide a complete report of adverse events and a listing of patients in the Phase 1b that were taken off treatment due to adverse events, and the cycles in which that occurred. During the Phase 2 study, a formal amendment will be considered if at any point the first course DLT rate exceeds 30%, inclusive of all Phase 1b/2 patients treated at the RP2D on the combination of Hu5F9-G4 (magrolimab) and mogamulizumab, and accrual will be held pending review. Additional toxicity monitoring rules beyond cycle 1 follow:

The grade 3-4 AE rate of mogamulizumab throughout multiple cycles of the MAVORIC study was 41% (75 of 184 patients), with 28/184 stopping for AE (15%). The median PFS was approximately 7.7 months. Two of the three on-treatment deaths with mogamulizumab single agent (sepsis and polymyositis) were considered treatment related (2 of 184).

The optimistic scenario is that the combination of Hu5F9-G4 (magrolimab) and mogamulizumab will have enhanced activity over single agent mogamulizumab offsetting the potential increased toxicity of the doublet over single agent mogamulizumab ab. It is expected that the toxicity will be higher with the doublet, and this will be further amplified if the combination is active, keeping patients on treatment longer and increasing the chance of cumulative toxicities and sporadic toxicities. As a result, the rules for toxicity monitoring throughout the study will trigger a Toxicity Monitoring Committee (TMC) meeting (members of the TMC will receive the report at the time of the trigger and will respond within two weeks of the report of the trigger) to decide upon further action based on the totality of the data on both arms. The Toxicity Monitoring Committee will have the authority to hold study accrual and will send a report to the Data Coordinating Center, which will also be reviewing severe adverse events and the totality of the data at the regularly scheduled intervals (every 6 months) [separate from the monthly data coordination center review of data]. The Toxicity Monitoring Committee will consist of the NCI drug monitor, the NCI disease monitor, the study PI and the site PI/treating physician, or the respective designees for the toxicity committee members.

The triggering rules for Toxicity Monitoring Committee are as follows:

1) Any treatment-related death on the combination of Hu5F9-G4 (magrolimab) and mogamulizumab (considered possibly related) will trigger a Toxicity Monitoring Committee meeting. The request for a Toxicity Monitoring Committee meeting will be made within 24 hours of the report of a treatment-related death to the Data Coordinating Center.
2) If the reported data documents at least 2 patients and more than 30% of patients stop therapy on the doublet due to adverse events before the third cycle, the Data Coordinating Center (which meets monthly) will trigger a Toxicity Monitoring Committee meeting. If

this rule is triggered, the Toxicity Monitoring Committee can hold accrual or permit continued accrual. If permitting continued accrual, the Toxicity Monitoring Committee will make a recommendation for continuing to monitor the off-treatment pattern after the first time this condition is triggered.

The Data Coordinating Center will compare the rate of AEs meeting DLT criteria (occurring at any point during treatment including outside of the DLT period) on both arms using an alpha-spending function approach with an O'Brien-Fleming monitoring boundary beginning at about 33% of the expected information (28 total patients). The second planned evaluation is at 56 total patients (2/3 information). The Data Coordinating Center will employ a one-sided type I error of 0.15 (spending 0.044 alpha at 28 patients and the remainder at 56 patients). A statistically significant increase in the rate of AEs on the doublet arm by these rules will result in the Data Coordinating Center calling for a Toxicity Monitoring Committee. For example, there is greater than a 70% chance of triggering this review if the cumulative rate of AEs meeting the DLT criteria in the control arm is 41% and the cumulative rate in the doublet arm is 62%. As a further example, this rule will be triggered if the cumulative rate of DLT-level AEs (over all cycles) is 5/14 vs 10/14 for the SOC vs doublet arm and will also be triggered for 11/28 (39%) vs 16/28 (57%) AEs on the respective arms. Once triggered, the Toxicity Monitoring Committee will have the same options as in item 2 above.

Analysis Plan: We will use a stratified Cochran-Mantel-Haenszel $\chi 2$ test to compare between-group differences in ORR6 proportion. The primary analysis will include all patients who begin treatment. Patients who do not have an assessment will be considered treatment failures for the ORR6 endpoint. We will also conduct a secondary analysis on the ITT population (all subjects randomized to a therapy and assigned a study number) and an efficacy evaluable set (all subjects who received the first 12 weeks of treatment and completed the week 12 response assessment).

9.2 Sample Size/Accrual Rate

Phase 1b: Sample size = 6-18 patients; accrual rate = 4 patients per month
Phase 2: Sample size = 82 patients; accrual rate = 4 patients per month

PLANNED ENROLLMENT REPORT

DOMESTIC PLANNED ENROLLMENT REPORT (TREATMENT)					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	3	5	0	0	8
Native Hawaiian or Other Pacific Islander	4	6	0	0	10
Black or African American	17	32	5	8	62
White	2	2	0	0	4
More Than One Race	1	1	0	0	2
Total	27	47	5	8	87

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INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT (TREATMENT)					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	0	1	0	0	1
More Than One Race	0	0	0	0	0
Total	0	1	0	0	1

9.3 Stratification Factors

The following stratification factors will be used:

1. Mycosis fungoides *vs* Sezary Syndrome
2. Stage 1B-2A *vs* Stage 2B-IV

9.4 Analysis of Secondary Endpoints

The analysis plan for the secondary objectives will be as follows:

Table 5: Analysis of Secondary Endpoints

Secondary Endpoint	Statistical Method
ORR, ORR4, ORR12	Chi-squared
PFS, DOR, TTNT	Kaplan-Meier method; Log- rank

9.5 Reporting and Exclusions

9.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with Hu5F9-G4 (magrolimab).

9.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, *etc.*). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

9.6 Data Safety Monitoring Board

The conduct of this study will be overseen by the ETCTN DSMB. The DSMB will be responsible for recommendations to the Principal Investigator and NCI regarding possible trial closure and/or early reporting of the study. The study team (with the exception of the study statistician) will not have access to the summary outcome data until released by the DSMB.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

10.1.1 CAEPR for CTEP IND Agent

10.1.1.1 CAEPR for Hu5F9-G4 (magrolimab)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Hu5F9-G4 (magrolimab, NSC 809249)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 579 patients*. Below is the CAEPR for Hu5F9-G4 (magrolimab).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, May 24, 2022[1]

Adverse Events with Possible Relationship to Hu5F9-G4 (Magrolimab) (CTCAE 5.0 Term) [n= 579]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Diarrhea		***Diarrhea (Gr 2)***
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Infusion related reaction			***Infusion related reaction (Gr 2)***
INVESTIGATIONS			
	Blood bilirubin increased		
	Platelet count decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hypomagnesemia		
NERVOUS SYSTEM DISORDERS			
	Headache		***Headache (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
	Rash acneiform		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Adverse events reported on Hu5F9-G4 (Magrolimab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Hu5F9-G4 (Magrolimab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia; Thrombotic thrombocytopenic purpura
GASTROINTESTINAL DISORDERS - Colitis; Mucositis oral
INFECTIONS AND INFESTATIONS - Sepsis
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Pain in extremity
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Rash maculo-papular

Note: Hu5F9-G4 (Magrolimab) in combination with other agents could cause an exacerbation of any adverse event

currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.1.2 CAEPR for Commercial Agent

10.1.2.1 CAEPR for Mogamulizumab

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
KW-0761 (mogamulizumab, NSC 791064)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. ***Frequency is provided based on 4759 patients.*** Below is the CAEPR for KW-0761 (mogamulizumab).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, September 15, 2019[1]

Adverse Events with Possible Relationship to KW-0761 (mogamulizumab) (CTCAE 5.0 Term) [n= 4759]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
CARDIAC DISORDERS			
		Chest pain - cardiac Myocardial infarction	
		Myocarditis[2]	
		Restrictive cardiomyopathy	
GASTROINTESTINAL DISORDERS			
	Nausea		***Nausea (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	Flu like symptoms[2]		
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		
		Anaphylaxis[3]	
		Immune system disorders - Other (graft versus host disease)[4]	
INFECTIONS AND INFESTATIONS			

Adverse Events with Possible Relationship to KW-0761 (mogamulizumab) (CTCAE 5.0 Term) [n= 4759]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Infection[5]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[3]		***Infusion related reaction[3] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased[2,6]		
	Alkaline phosphatase increased[2,6]		
	Aspartate aminotransferase increased[2,6]		
	Blood bilirubin increased[2,6]		
	GGT increased[2,6]		
	Lymphocyte count decreased[2]		***Lymphocyte count decreased[2] (Gr 2)***
	Neutrophil count decreased[2]		***Neutrophil count decreased[2] (Gr 2)***
	Platelet count decreased[2]		***Platelet count decreased[2] (Gr 2)***
	White blood cell decreased[2]		***White blood cell decreased[2] (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthritis[2]		
NERVOUS SYSTEM DISORDERS			
	Peripheral motor neuropathy[2]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme[2]	
	Rash maculo-papular[2]		***Rash maculo-papular[2] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (drug eruption, toxic skin eruption)[2]	
	Skin hypopigmentation[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis[2]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-mediated adverse reactions have been reported in patients receiving KW-0761 (mogamulizumab). Adverse events potentially related to KW-0761 (mogamulizumab) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of KW-0761 (mogamulizumab), administration of corticosteroids and supportive care.

[3]Infusion reactions, including high-grade hypersensitivity reactions, anaphylaxis, and cytokine release syndrome, which have been observed following administration of KW-0761 (mogamulizumab), may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of KW-0761 (mogamulizumab).

[4]Acute graft-versus-host disease has been observed in patients treated with KW-0761 (mogamulizumab) who subsequently received hematopoeitic stem cell transplants.

[5]Infection may include any of the infection sites under the INFECTIONS AND INFESTATIONS SOC.

[6]Symptoms of hepatic dysfunction may include Alanine aminotransferase increased, Alkaline phosphatase increased, Aspartate aminotransferase increased, Blood bilirubin increased, and GGT increased under the INVESTIGATIONS SOC.

Adverse events reported on KW-0761 (mogamulizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that KW-0761 (mogamulizumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Disseminated intravascular coagulation; Febrile neutropenia; Hemolysis; Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Atrial fibrillation; Sinus tachycardia; Supraventricular tachycardia
EYE DISORDERS - Retinal vascular disorder
GASTROINTESTINAL DISORDERS - Abdominal pain; Cheilitis; Colitis[2]; Constipation; Diarrhea; Gastritis; Mucositis oral; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema limbs; Generalized edema; Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (bile duct stone); Hepatobiliary disorders - Other (hepatitis)
INVESTIGATIONS - Blood lactate dehydrogenase increased[2]; CPK increased; Lipase increased; Serum amylase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Acidosis; Anorexia; Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (diabetes mellitus)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Flank pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (tendonitis); Myositis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Depressed level of consciousness; Encephalopathy; Headache; Nervous system disorders - Other (altered state of consciousness); Nervous system disorders - Other (cerebellar syndrome); Paresthesia; Seizure
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Cough; Dyspnea; Hypoxia; Pleural effusion; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Erythroderma; Hyperhidrosis; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (lichenoid keratosis); Urticaria
VASCULAR DISORDERS - Hypertension[2]; Hypotension[2]

Note: KW-0761 (mogamulizumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version

5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 Expedited Adverse Event Reporting

10.3.1 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of Adverse Events (AEs) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. Sites must initiate all AEs for this study in Medidata Rave.

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational study agent/intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- AEs are recorded and complete (no missing fields) and the form is query-free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the

box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: *Protocols > Documents> Protocol Related Documents> Adverse Event Reporting*, and
- Additional resources: *Resources > CTSU Operations Information> User Guides & Help Topics*.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

10.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

10.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality as long as the death occurred within 30 days after the last administration of the investigational agent. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the

system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

10.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 10.3):

CTCAE SOC	Adverse Event	Grades	≥24h Hospitalization[a]
Investigations	Lymphocyte count decreased	1-4	Regardless

[a] Indicates that an adverse event required hospitalization for ≥24 hours or prolongation of hospitalization by ≥24 hours of a patient.

10.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

10.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

10.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

11. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	Priming	Cycle 1[m]				Cycle 2[m]				Cycle 3[m]		Cycle 4-12[n]		End of Treatment or Progression[a]
		Wk 1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 3	Wk 1	Wk 3	
Hu5F9-G4 (magrolimab)		A	A	A	A	A	A	A	A	A	A	A	A	A	
Mogamulizumab			B	B	B	B	B		B		B	B	B	B	
Informed consent	X														
Demographics	X														
Medical history	X														
Concurrent meds[b]	X----------														X
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Height	X														
Weight	X	X	X				X				X		X		
Performance status[c]	X	X	X	X	X	X	X		X		X		X		X
CBC w/diff, plts[p]	X	X[p]	X[p]	X	X	X	X	X	X	X	X	X	X		
Comprehensive Chemistry Panel[d]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy test[e]	X														
ABO/Rh type and screen, DAT[l]	X														
Antibody Screen[l]	X														
Extended RBC phenotyping including minor antigens such as CcDEe, Cw, MNSs, Kk, FyaFyb, and Jka Jkb[l, q]	X														
Adverse event evaluation		X----------											----------X		X
mSWAT assessment/medical photography[f]		X					X					X	X[f]		X
Imaging[g]	X											X[g]	X[g]		X[g]
Flow Cytometry		X										X[h]	X[h]		X[h]
FFPE biopsy tissue (optional)	X[o]														
Skin punch biopsies[j]	X			X								X			X
Correlative blood collection[k]	X			X								X	X		X

	Pre-Study	Priming	Cycle 1[m]				Cycle 2[m]				Cycle 3[m]		Cycle 4-12[n]		End of Treatment or Progression[a]
		Wk 1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 3	Wk 1	Wk 3	

A: *Hu5F9-G4 (magrolimab):* On Priming Week 1 only, a priming dose of 1 mg/kg Hu5F9-G4 (magrolimab) will be given. Then assigned dose on Cycle 1 Day 1, 8, 15, and 22, Cycle 2 Day 1, 8, 15 and 22, Cycle 3+ Day 1, 15. Cycles are 28 days long.

B: Mogamulizumab: 1mg/kg on Cycle 1 Day 1, 8, 15, and 22, Cycle 2+ Day 1, 15. Cycles are 28 days long.

a: Off-study evaluation. Cycle 12 (Week 48) visit may serve as end of treatment/progression visit

b: Starting from cycle 4, concurrent meds will be evaluated first week of every cycle

c: Note: Performance status evaluations are based on a 4 week cycle. At minimum, performance status should be evaluated at the beginning of every cycle.

d: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

e: Pregnancy test for women of childbearing potential.

f: Starting from Cycle 6, mSWAT assessment will be performed on the 1st week of every 3rd cycle (i.e. cycle 6, 9, 12, 15, etc.), and at the end of treatment or progression.

g. **Patients without extracutaneous disease at screening (N0-2 and M0):** scans will be performed at baseline and repeated to confirm global PR/CR, at suspicion of PD. **Patients with extracutaneous disease at screening (N3 or Nx or M1):** scans will be performed at baseline, Week 12, and then repeated at the end of every 3 cycles (i.e. cycle 6, 9, 12.), to confirm global PR/CR, at suspicion of PD. Scans at the time of progression or at the end of treatment do not need to be repeated if the most recent scan occurred within the past 28 days. End of cycle scans should be performed between Days 15 and 28, or Day 1 of the following cycle. Either PET/CT or diagnostic CT chest/abdomen/pelvis +/- neck may be used. Visit windows of ± 7 days allowed.

h. **Patients with B1 or B2 disease at baseline:** Flow cytometry will be performed at Week 1, Week 12, and then repeated on the 1st week of every 3rd cycle (i.e. cycle 6, 9, 12). Flow cytometry will also be performed to confirm global PR/CR, if progression of disease is suspected and at end-of-treatment. **Patients with B0 disease at baseline:** Flow cytometry will be performed at baseline, to confirm a partial or complete response, if progression of disease is suspected, and at end-of-treatment.

j. Biopsies are not required for patients with a complete response in the skin.

k. Correlative blood collection will be performed at baseline, Cycle 1 Week 2, Cycle 3 Week 3, Cycle 6 Week 1, and at PD/EOT.

l. ABO/Rh, RBC genotyping, and DAT testing are not required for patients randomized to the mogamulizumab-only arm. This will be done prior to crossover to the combination arm if applicable.

m. For cycle 1 through cycle 3, visit windows of ± 2 days allowed

n. Starting from cycle 4, visit windows of ± 3 days allowed

o. Archival tissue sample within 6 months prior to registration

p. Within 24 hours prior to each of the first 2 doses of Hu5F9-G4infusion, patients must have a documented hemoglobin level of ≥9 g/dL. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet the minimum hemoglobin threshold prior to administering each of the first 2 doses of Hu5F9-G4. An additional hemoglobin must be checked 3 to 6 hours after the initiation of the first and second doses of Hu5F9-G4. 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.

q. RBC genotyping 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). This may be performed for all patients in lieu of an extended RBC phenotyping.

12. MEASUREMENT OF EFFECT

Although the clinical benefit of these drugs has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every 12 weeks.

12.1 Antitumor Effect – ISCL/USCLC/EORTC Response Criteria for Mycosis Fungoides and Sezary Syndrome

12.1.1 Definitions

Evaluable for Adverse Events. All patients will be evaluable for adverse event evaluation from the time of their first treatment.

Evaluable for Response. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of Cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

Response and progression will be evaluated in this study using the 2011 ISCL/USCLC/EORTC Response Criteria for Mycosis Fungoides and Sezary Syndrome (Olsen *et al*., 2011).

12.1.2 Response and Evaluation Endpoints

The consensus response criteria for Mycosis Fungoides and Sezary Syndrome incorporates evaluation of skin, blood, lymph node, and visceral disease compartments.

Skin. Skin lesions and erythema will be evaluated using the mSWAT. During each mSWAT assessment, medical photography should be completed as described in Appendix F. Digital copies of the photographs will be retained at sites for quality assurance or secondary review purposes. The mSWAT is an objective, quantitative, severity-weighted method to assess the extent of skin lesions. An mSWAT score is derived by measuring each lesion as a percentage of total body surface area (%TBSA) and multiplying it by a severity-weighting factor (1 = patch, 2 = plaque, 4 = tumor). All individual numbers are then added to produce a total score. The mSWAT assessment tool is described in Appendix E.

Blood. Peripheral blood flow cytometry will be used to evaluate circulating malignant T-cells as indicated on the Study Calendar. Flow cytometry will be performed by each institution's standards.

Lymph nodes and Viscera. Either PET/CT or contrast-enhanced CT of the chest, abdomen, and pelvis (+/- neck as clinically indicated) may be used to evaluate response in lymph nodes and viscera. Investigators should utilize the same imaging modality performed for the baseline assessment throughout the trial. Although PET/CT may be utilized, response assessment is

performed through sum of the product of diameters for measureable lesions and therefore it is encouraged to also obtain a diagnostic CT along when PET imaging is performed.
The Investigator will identify, prospectively, the lesions to be followed to evaluate the subject's response to therapy. Lymph nodes must be > 15 mm in the long axis (greatest transverse diameter, GTD) or > 10 mm in the short axis if the GTD is > 10 to ≤ 15 mm. Lymph node biopsies may be performed, at the discretion of the Investigator, to rule out inflammation or to confirm disease. Analysis of these biopsies will be done by the pathologist at the study site.

12.1.3 Response Criteria

Response in each compartment will be assessed by the following criteria.

Response in Skin*

Complete response (CR)	100% clearance of skin lesions[#]
Partial response (PR)	50-99% clearance of skin disease from baseline without new tumors (T_3) in subjects with T_1, T_2 or T_4 only skin disease
Stable disease (SD)	<25% increase to <50% clearance in skin disease from baseline without new tumors (T_3) in subjects with T_1, T_2 or T_4 only skin disease
Progressive disease (PD)[†]	(1) >25% increase in skin disease from baseline or (2) New tumors (T_3) in subjects with T_1, T_2 or T_4 only skin disease or (3) Loss of response: in those with CR or PR, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with CR

*Based on mSWAT score.
A biopsy of normal appearing skin is unnecessary to assign a CR. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease where otherwise a CR would exist. If histologic features are suspicious or suggestive of Mycosis Fungoides/Sézary Syndrome (see histologic criteria for early MF7), the response should be considered a PR only.
[†]Whichever criterion occurs first.

Response in Blood*

CR*	B_0
PR**	>50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR or PD
PD[†]	(1) B_0 to B_2 or (2) >50% increase from baseline and at least 5,000 neoplastic cells/μL or (3) Loss of response: in those with CR who were B_1 or B_2 at baseline, increase in neoplastic >1000 neoplastic cells/ μL or in those with PR who were originally B_2 at baseline, >50% increase from nadir and at least 5,000 neoplastic cells/μL
Relapse	Increase of neoplastic blood lymphocytes to ≥B_1 in those with CR

* As determined by absolute numbers of neoplastic cells/uL.

** There is no PR in those with B1 disease at baseline as the difference within the range of neoplastic cells that define B1 is not considered significant and should not affect determination of global objective response.

†Whichever occurs first.

Response in Lymph Nodes*

CR	All lymph nodes are now <1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma. In addition, lymph nodes that were N3 classification and <1.5 cm in long axis diameter at baseline, must now be <1 cm in diameter of the short axis or biopsy negative for lymphoma
PR	(1) Cumulative reduction >50% of the SPD [sum of the maximum linear dimension (major axis) x longest perpendicular dimension (minor axis) of each abnormal lymph node at baseline and no new lymph node >1.5 cm or >1.0 cm in the short axis if long axis 1-1.5cm diameter.
SD	Fails to attain the criteria for CR, PR and PD
PD†	(1) >50% increase in SPD from baseline of lymph nodes or (2) Any new node >1.5 cm in greatest transverse diameter or >1 cm in short axis diameter if 1-1.5 cm in long axis that is proven to be N3 histologically or (3) Loss of response: in those with PR or CR, >50% increase from nadir in SPD of lymph nodes
Relapse	Any new lymph node >1.5cm in long axis diameter in those with CR

* Peripheral and central lymph nodes.

†Whichever criterion occurs first.

Response in Viscera

CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging. No nodules should be present on imaging of liver or spleen. Any post treatment mass must be determined to be biopsy to be negative for lymphoma
PR	>50% regression in any splenic or liver nodules, or in measurable disease (SPD) in any organs abnormal at baseline. No increase in size of liver or spleen and no new sites of involvement.
SD	Fails to attain the criteria for CR, PR or PD
PD†	(1) >50% increase in size (SPD) of any organs involved at baseline or (2) New organ involvement or (3) Loss of response: in those with PR or CR, >50% increase from nadir in the size (SPD) of any previous organ involvement
Relapse	New organ involvement in those with CR

†Whichever criterion occurs first.

Global Response: The global response incorporates response assessments from all disease compartments.

Global Response Score

Global Score	Definition	Skin	Nodes	Blood	Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI		
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD		
		PR	No category has a PD and if any other category involved at baseline, at least one has a CR or PR		
SD	Failure to attain CR, PR or PD representative of all disease	PR	No category has a PD and if any other category involved at baseline, no CR or PR in any		
		SD	CR/NI, PR, SD in any category and no category has a PD		
PD	Progressive disease	PD in any category			
Relapse	Recurrence disease in prior CR	Relapse in any category			

NI= noninvolved

12.1.4 Confirming early progression:

Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. In cutaneous lymphoma this may manifest as worsening appearance of skin lesions or lymph nodes early in treatment. To allow sufficient time to differentiate such pseudoprogression from true progression, patients with early progression events may continue on treatment with increased surveillance until true progression is confirmed. Treatment beyond progression in such cases can occur at the investigator's discretion after approval by the Principal Investigator.

Skin progression: Patients with progression in the skin compartment documented any time up to, and including, their assessment at 12 weeks may continue on treatment if they meet all of the following criteria:

1. Progression cannot be due to development of new tumors (T3) disease in a patient with T1, T2, or T4 disease
2. Patients must have monthly mSWAT assessments while continuing treatment
3. During this period of unconfirmed progression, the mSWAT score on each subsequent assessment must be less than or equal to the most recent mSWAT score (i.e. the mSWAT must improve with each subsequent evaluation)

It is strongly encouraged that a skin biopsy be performed if the investigator suspects pseudoprogression in the skin. The patient may continue with monthly mSWAT examinations until Cycle 6. By Cycle 6, the patient must meet criteria for stable disease or better to continue on treatment. If progression is confirmed by an increase in mSWAT in a subsequent evaluation, then the date of progression for endpoint analysis will be the first date of progression, not the

date of the confirmation.

Lymph node: Patients with progression in the lymph node compartment documented on their first scheduled assessment at 12 weeks may continue on treatment if they meet the following criteria:

1. Either a biopsy must be performed of a progressing lymph node (preferred), or a repeat scan must be performed in 4-8 weeks after the week 12 scan showing progression
2. If a biopsy is performed on a progressing lesion, it must show changes consistent with pseudoprogression.
3. If a biopsy cannot be performed, then a subsequent scan performed 4-8 weeks later must have an SPD less than or equal to the week 12 scan. If progression was due to the appearance of new assessable lymph nodes, all new lymph nodes must be equal or smaller in cross-sectional area to their measurements on the week 12 scan

If a follow up scan performed 4-8 weeks later shows improvement, then the patient can continue on the treatment protocol until the next planned assessment at Cycle 6. All patients must have a lymph node response of SD or better on their Cycle 6 imaging assessment to continue on treatment protocol.

If progression is confirmed by imaging evaluation on either the scan performed 4-8 weeks later or their Cycle 6 imaging, then the date of progression for endpoint analysis will be the first date of progression, not the date of the confirmation scan.

If the repeat evaluations do not confirm progression, the patient will continue to be treated and evaluated as per the original study calendar.

12.2 Definitions of Study Endpoints

Overall Response Rate (ORR): ORR is defined as the proportion of patients who have a partial or complete response to therapy as defined by the global response score.

Duration of Response (DOR): DOR is defined as the duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrence or PD is objectively documented.

Overall Response Rate 4 (ORR4): ORR4 is defined as the proportion of patients who have a partial or complete response to therapy AND a duration of response ≥ 4 months.

Overall Response Rate 6 (ORR6): ORR6 is defined as the proportion of patients who have a partial or complete response to therapy AND a duration of response ≥ 6 months.

Overall Response Rate 12 (ORR12): ORR12 is defined as the proportion of patients who have a partial or complete response to therapy AND a duration of response ≥ 12 months.

Progression-Free Survival (PFS): PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Time to next treatment (TTNT): TTNT is defined as the duration of time from the start of treatment on this protocol to time of the next anti-neoplastic therapy.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

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

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

For a Phase 1/2 trial, enrollment to the Phase 2 portion of the trial will not begin until a protocol amendment has been submitted which summarizes the Phase 1 results, the recommended Phase 2 dose, and the rationale for selecting it. The amendment must be reviewed and approved by CTEP before enrollment to the Phase 2 portion can begin.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

13.2 Data Reporting

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.
Requirements to access Rave via iMedidata:

- Active CTEP registration with credentials necessary to access secure NCI/CTSU IT systems, and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.
  Rave role requirements:
  - Rave CRA or Rave CRA (Lab Admin) role, must have a minimum of an Associate Plus (AP) registration type,
  - Rave Investigator role, must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR), and
  - Rave Read Only or Rave SLA role must have at a minimum an Associates (A) registration type.
- Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

If the study has a Delegation of Tasks Log (DTL), individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory applicatin, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management > Rave Home* and click to accept the invitation in the Tasks pane located in the upper right-corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site

audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

13.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

13.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available on the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

13.4 CTEP Multicenter Guidelines

N/A

13.5 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study.

Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and

comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13.6 Genomic Data Sharing Plan

We will share anonymized genomic sequence data (whole exome sequencing and RNA sequencing) from all subjects by depositing these data in the database of Genotypes and Phenotypes (dbGaP) (a controlled-access database funded by NIH). The genotype data will be made publicly available no later than the date of initial publication or twelve months after completion of sequencing.

13.7 Incidental/Secondary Findings Disclosure Procedure

There are no planned analysis to detect medically important genomic features other than potential biomarkers for the protocol therapies. There will be no planned disclosure of incidental/secondary genomic findings. The informed consent form will disclose that the subject will not be contacted about potential medically important findings.

14. CALIFORNIA CANCER CONSORTIUM (CCC) POLICIES FOR MONITORING CONSORTIUM TRIALS

This protocol is monitored at several levels, as described in this section. To summarize: The trial PI has access to the data at all times. The CCC Data Coordinating Center reviews accrual and toxicities monthly. An external, independent DSMC reviews the study progress twice yearly. In addition, for the Phase 1 portion, the study PI will have monthly, and as needed, conference calls with study investigators to review accrual, progress, and any unforeseen issues. Dose escalation/expansion/de-escalation decisions require sign-off by the study PI (or his or her designee) and study statistician (or his or her designee). During the Phase 2 portion, the study PI will have quarterly, and as needed, conference calls with study investigators and CTEP Medical Officer(s) to review accrual, progress, pharmacovigilance, and any unforeseen issues. Decisions to proceed to the second stage of the Phase 2 trial will require sign-off by the study PI and the trial statistician.

The protocol PI is responsible for monitoring the conduct and progress of this Phase 2 trial, including the ongoing review of accrual, data, and toxicities, as well as the accumulation of reported AEs from other trials testing the same drugs. The participating clinicians and their designees are responsible for timely submission of AE reports (see Section 10.0) and electronic CRFs. The Data Coordinating Center for the CCC Consortium is responsible for providing the PI with access to the submitted CRF data in summary and detail in a timely fashion. Although the PI is responsible for evaluating the cumulative reported AEs and the impact that these have on the continued conduct of the trial, it is the Data Coordinating Center of the CCC that distributes all submitted SAE reports to the appropriate individuals, including the local protocol PIs, at each of the participating institutions.

The Data Coordinating Center posts a summary (accrual, toxicities, and responses) of each CCC initiated trial on the CCC website. In this way, each PI has access to up-to-date information on the status of his or her trial. In consultation with the collaborating statistician, the PI is responsible for review of:

- for Phase 1 trials, all DLTs and decisions regarding dose escalation, expansion, as well as decisions to terminate escalation, and
- for Phase 2 trials, the toxicities and therapeutic endpoints referred to in the statistical plan.

The Data Coordinating Center meets monthly to review data management and data quality issues, including completeness of data submissions and accuracy in terms of built-in, computerized logic checks. Any issues identified, and subsequent corrective plans are presented to the Internal Committee and at the next CCC teleconference meeting for review and approval.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

Formulas to estimate renal function using serum creatinine provided by the NCI's Investigational Drug Steering Committee (IDSC) Pharmacological Task Force in table below.

1. Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg\ /\ dL)} \{\times 0.85\ for\ female\ patients\}$$

Followed by conversion to a value normalized to 1.73 m^2 with the patient's body surface area (BSA).

References

1. Cockcroft, D.W. and M.H. Gault. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*. 16:31-41.

APPENDIX C: PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Blood Type:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: 10384

Study Drug(S):
Hu5F9-G4 (magrolimab)
Mogamulizumab

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

APPENDIX D TISSUE BIOPSY VERIFICATION

A completed copy of this appendix (i.e., Tissue Biopsy Verification) must be submitted to the EET Biobank.

Note: If this information is not provided with the biopsy specimen, then it will not be accepted by the EET Biobank.

Please have the Clinician* responsible for signing out this patient's case complete the following:

ETCTN Universal Patient ID: _____

ETCTN Patient Study ID: _____

Date of Procedure (mm/dd/yyyy): _____

Tissue Type (circle one): Skin

Time point (circle one): Baseline C1W2 C3W3

End of Treatment/Progression

Site(s) Tissue Taken From: _____

Diagnosis: _____

I agree that this tissue may be released for research purposes only and that the release of this tissue will not have any impact on the patient's care.

_____ _____
Clinician Signature Date

_____
Clinician Printed Name

*Note: For the purposes of this form, Clinician could include the Nurse Practitioner, Registered Nurse, Pathologist, Radiologist, Interventional Radiologist, Surgeon, Oncologist, Internist, or other medical professional responsible for the patient's care.

APPENDIX E: MODIFIED SEVERITY-WEIGHTED ASSESSMENT TOOL (MSWAT)

The mSWAT is an objective, quantitative, severity- weighted method to assess the extent of Mycosis Fungoides lesions. A SWAT score is derived by measuring each lesion as a percentage of total body surface area (%TBSA) and multiplying it by a severity-weighting factor (1 = patch, 2 = plaque, 4 = tumor). All individual numbers are then added to produce a total score.

The body is divided into 12 regions with pre-assigned %TBSA based on methodology used to assess burns. The extent of skin disease is assessed for each region and quantified by using the subject's palm as a "ruler" to measure the %TBSA involvement within each region.

Subject's palm with 4 fingers, including the thumb and measured from wrist to fingertips, is 1% of TBSA.

Subject's palm without fingers is 0.5% of TBSA.

Modified Severity Weighted Assessment Tool

Modified Severity Weighted Assessment Tool

Mycosis Fungoides lesion type	**Elevation description**	**Erythema description**
Patch	Abnormal skin not elevated from normal skin	Flat erythema or erythema with mild infiltration
Plaque	Abnormal skin elevated from normal skin by <5 mm	Elevated erythema or erythema with moderate infiltration
Tumor	Abnormal skin elevated from normal skin by ≥5 mm	Erythema with fissuring, ulceration, or tumor

SWAT Score Calculation

Sum of %TBSA from all body regions affected by patches x severity weighted factor of 1

+ Sum of %TBSA from all body regions affected by plaques x severity weighted factor of 2

+ Sum of %TBSA from all body regions affected by tumors x severity weighted factor of 4

= TOTAL SWAT: (maximum score = 400)

Modified Severity Weighted Assessment Tool

Body region (%BSA)	Patch*	Plaque*	Tumor*
Head (7%)			
Neck (2%)			
Anterior trunk (13%)			
Arms (8%)			
Forearms (6%)			
Hands (5%)			
Posterior trunk (13%)			
Buttocks (5%)			
Thighs (19%)			
Legs (14%)			
Feet (7%)			
Groin (1%)			
Subtotal of lesion BSA			
Weighting factor	x1	x2	x4
Subtotal lesions BSA x weighting factor			
mSWAT score (summation of each column line above) =			

patch = any size lesion without induration or significant elevation above the surrounding uninvolved skin: poikiloderma may be present.

plaque = any size lesion that is elevated or indurated; crusting, ulceration or poikiloderma may be present.

tumor = any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

APPENDIX F: STANDARDIZED MEDICAL PHOTOGRAPHY

Using a standard medical blue background and with the patient in anatomical position (palms placed anteriorly), the following photos will be taken of the study participant:

1. Global (full body).

2. Half-global (half body – anterior and posterior aspect).

3. Additional photographs will be taken at a short distance (1 foot) of biopsy sites.