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NCI Pediatric Early Phase Clinical Trials Network

A program funded by the National Cancer Institute of the National Institutes of Health

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February 2, 2024

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National Cancer Institute
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Dear Ms. Kruhm,

Enclosed please find Amendment #8 to protocol PED-CITN-03, Phase 1 Trial of Hu5F9-G4 (magrolimab) combined with dinutuximab in children and young adults with relapsed and refractory neuroblastoma or relapsed osteosarcoma.

Amendment #8 is in response to a request for a rapid amendment from Dr. Helen Chen (helen.chen@nih.gov). The amendment provides new and/or modified risk information associated with hu5F9-G4 and revises the Comprehensive Adverse Events and Potential Risks (CAEPR) list. Sections of the protocol and consent were updated to reflect these changes.

Administrative changes have been made; specific changes are detailed in the Summary of Changes table below. Minor administrative updates (such as the correction of typographical errors, spelling, or updates to the numbers of referenced sections) are tracked in the protocol but not specified.

Please let me know if you have any questions or need additional information.

Sincerely,

Emma Archuleta, Protocol Coordinator (for)
Robbie G. Majzner, PED-CITN-03 Study Chair,
Brenda Weigel, M.D., PEP-CTN Chair

SUMMARY OF CHANGES: PROTOCOL

In accordance with the above discussion, the following specific revisions have been made to the protocol.
Additions are in boldfaced font and deletions in ~~strikethrough~~ font.

#	Section	Page(s)	Change
1.	General	All	Updated protocol version date in the footer.
2.	Cover Page	1	Updated version date and amendment number.
3.	Contact Information	1 9	Updated study committee information
4.	Table of Contents	5-8	Updated for re-pagination.

5.	10.1.1.1	86-87	The CAEPR has been updated to (Version 2.2, December 6, 2023) in response to a rapid request for amendment:
			• Added New Risk:
			  • Likely: Hypotension
			  • Less Likely: Abdominal pain; Arthralgia; Cough; Dizziness; Generalized edema; Hypokalemia; Lymphocyte count decreased; Lung infection; Neutrophil count decreased; Pruritis; White blood cell count decreased
			  • Rare but Serious: Blood and lymphatic system disorders - Other (red blood cell agglutination); Hemolysis
			  • Also Reported on Hu5F9-G4 Trials But With Insufficient Evidence for Attribution: Alkaline phosphatase increased; Aspartate aminotransferase increased; Conjunctivitis; Constipation; Edema cerebral; Epistaxis; Hypertension; Hypophosphatemia; Intracranial hemorrhage; Tumor pain; Nervous system disorders - Other (cerebral hemorrhage); Pain; Pneumonitis; Serum sickness; Small intestinal obstruction; Thromboembolic event; Urinary tract infection
			• Increase in Risk Attribution:
			  • Changed from Less Likely to Likely: Fatigue
			  • Changed to Less Likely from Also Reported on Hu5F9-G4 Trials But With Insufficient Evidence for Attribution: Back pain; Dyspnea; Febrile neutropenia
			  • Changed to Rare but Serious from Also Reported on Hu5F9-G4 Trials But With Insufficient Evidence for Attribution: Sepsis
			• Decrease in Risk Attribution:
			  • Changed from Less Likely to Also Reported on Hu5F9-G4 Trials But With Insufficient Evidence for Attribution: Dry Skin; Hypomagnesemia; Rash acneiform

			• Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements: • Added: Abdominal pain Anorexia; Blood bilirubin increased Febrile neutropenia; Hypokalemia; Lymphocyte count decreased, Neutrophil count decreased, Platelet count decreased, White blood cell decreased

Activated: 04/16/2021
Closed:

Version Date: 02/02/2024
Amendment: 8

PED-CITN-03

Phase 1 Trial of Hu5F9-G4 (magrolimab) combined with dinutuximab in children and young adults with relapsed and refractory neuroblastoma or relapsed osteosarcoma

Lead Organization: COG Pediatric Early Phase Clinical Trials Network (PEP-CTN)

NCI Supplied Agents: Hu5F9-G4 (magrolimab); NSC 809249,Dinutuximab, NSC 764038, IND # IND Sponsor for Hu5F9-G4 (magrolimab) and Dinutuximab: DCTD, NCI

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CONTACT INFORMATION		
For Regulatory Requirements:	**For patient enrollments:**	**For Data Submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878) or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN can be accessed at https //www.ctsu.org/OPEN_SYSTEM/ or https //OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions.
The most current version of the **study protocol** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program – Identity and Access Management (CTEP-IAM) registration system and requires logging in with a CTEP-IAM username and password or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users).. Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website..		
For clinical questions *(i.e.*, patient eligibility or treatment-related) Contact the PI of the Lead Protocol Organization		
For nonclinical questions (*i.e.*, unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org		

SCHEMA

Figure 1: Overall Trial Schema

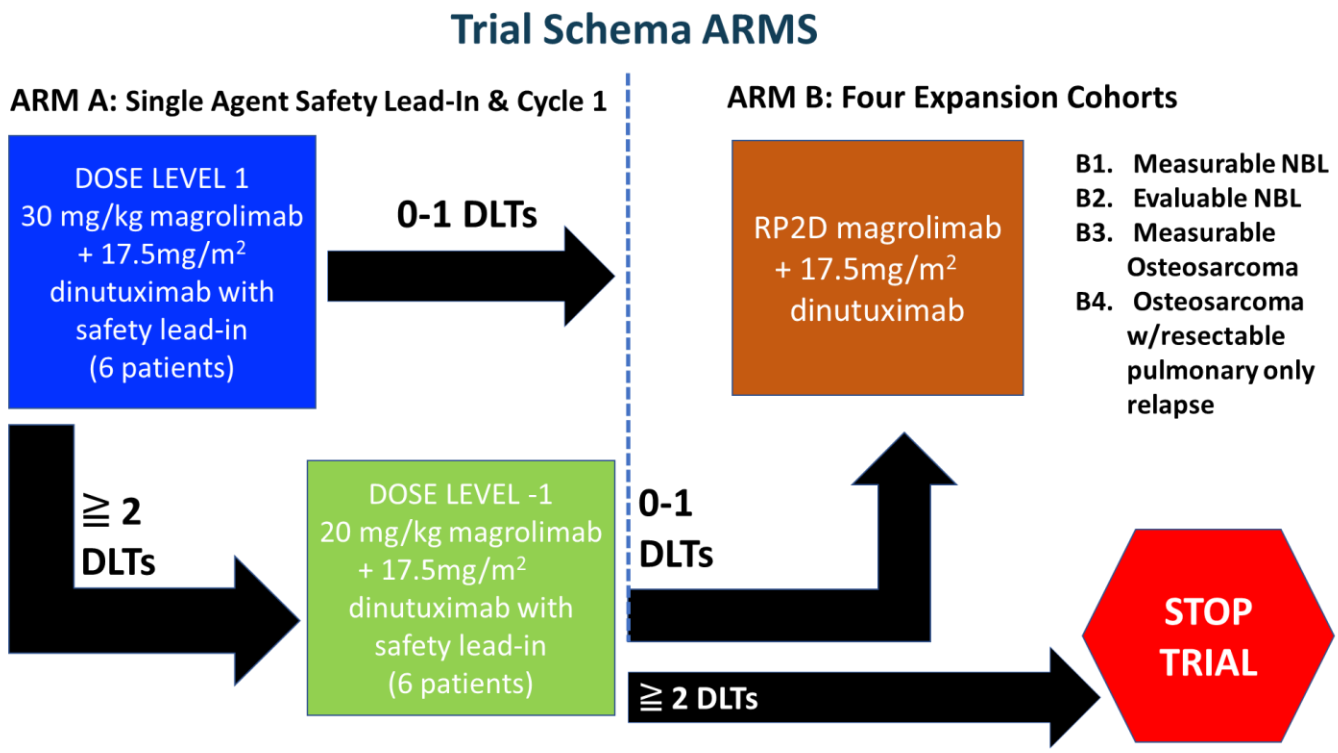
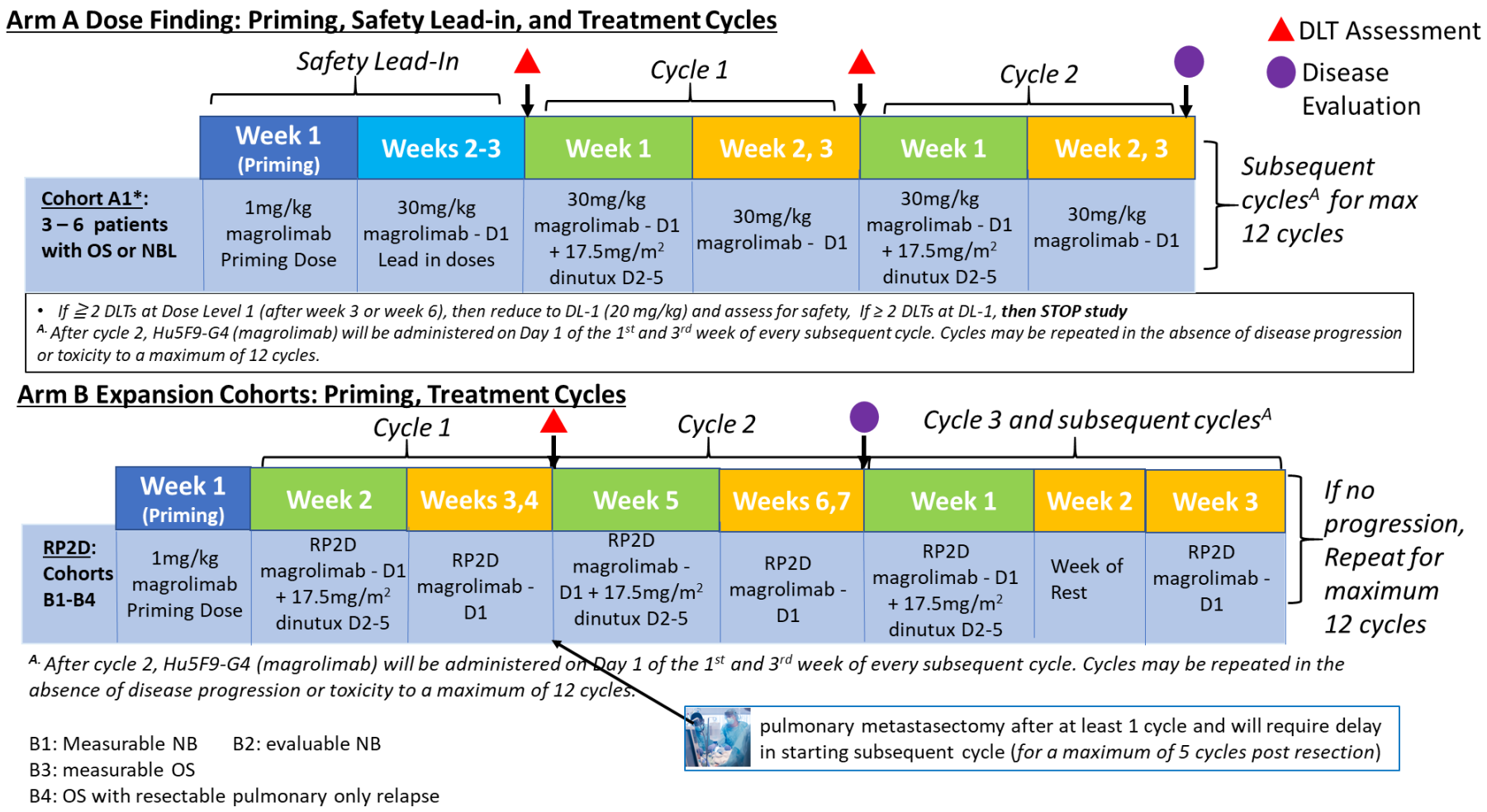


Figure 2: Trial Schedule Schema



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AGENT	NSC#	Supplier
Hu5F9-G4	809249	NCI
(magrolimab)	764038	NCI
Dinutuximab		

IND Number:
IND Sponsor: CTEP

This trial is covered by a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about your subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.
The Certificate of Confidentiality will not protect against mandatory disclosure by the researchers of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

1 OBJECTIVES

1.1 Primary Objectives

1.1.1 Determine the safety and tolerability of Hu5F9-G4 (magrolimab) in combination with dinutuximab in children and young adults with relapsed/refractory (R/R) neuroblastoma (NBL) or relapsed osteosarcoma.

1.1.2 Determine the recommended phase 2 dose (RP2D) of Hu5F9-G4 (magrolimab) given in combination with dinutuximab in children and young adults.

1.1.3 Determine the safety and feasibility of administering Hu5F9-G4 (magrolimab) in combination with dinutuximab to patients that undergo pulmonary resection of metastatic osteosarcoma within three weeks of surgery.

1.2 Secondary Objectives

1.2.1 Determine the pharmacokinetics (PK) of Hu5F9-G4 (magrolimab) in children and young adults.

1.2.2 Evaluate the Event Free Survival (EFS) in two cohorts of patients who are treated at the recommended phase 2 dose (RP2D) (measurable relapsed osteosarcoma and patients with pulmonary relapse undergoing resection) and compare to historical controls (Lagmay et al., 2016).

1.2.3 Observe and record anti-tumor activity.

1.2.4 Evaluate the Overall Response Rate (ORR) of patients in the NBL cohorts (Measurable R/R NBL and Evaluable R/R NBL) and osteosarcoma patients (measurable relapsed osteosarcoma) in the expansion cohorts treated at the RP2D.

1.3 Exploratory Objectives

1.3.1 To explore biomarkers of response and resistance including genomic (CD47 expression, FcR polymorphisms, SIRPa polymorphisms, and KiR phenotype) and immunologic (dinutuximab HACA, magrolimab ADA, peripheral and bone marrow immune subsets, and circulating cytokines).

1.3.2 To explore biomarkers of response in the tumor microenvironment through MIBI on resected tissue or archival tissues including comparison of pre- and post- treatment tumor tissues from patients undergoing staged resection of pulmonary osteosarcoma.

2 BACKGROUND

2.1 Introduction and Rationale

2.1.1 Relapsed and Refractory Osteosarcoma and Neuroblastoma (NBL) in Children and Young Adults

Children diagnosed with metastatic or relapsed solid tumors have few therapeutic options and often die from their disease (Perkins, Shinohara, DeWees, & Frangoul, 2014), (Ceschel et al., 2006). Despite the use of multiagent chemotherapy along with radiation and surgery, survival rates for patients with most high-risk solid tumors have not significantly improved since the 1980's. This is most evident for osteosarcoma, a bone tumor occurring in children, for which there has been little improvement in overall survival for the past forty years. Adding chemotherapeutic agents such as Ifosfamide to already intense chemotherapy regimens has not resulted in a survival benefit (Meyers et al., 2008). This is emblematic of pediatric high-risk solid tumors in general, as the success of multi-agent chemotherapy in pediatric oncology appears to be reaching a plateau. The sole solid tumor exception to this trend is neuroblastoma, where the adoption of anti-GD2 monoclonal based immunotherapy into frontline protocols has significantly increased overall survival rates among high risk patients (Yu et al., 2010). However, despite the use of anti-GD2 antibodies, more than forty percent of neuroblastoma patients ultimately die from their disease.

2.1.2 Neuroblastoma and Targeting GD2

Neuroblastoma, a tumor that arises from neural crest cells, occurs almost exclusively in children and accounts for 10-15% of pediatric cancer deaths. Approximately half of neuroblastoma patients are diagnosed with high risk disease (loosely defined as metastatic disease in children >18 months). These patients undergo intensive chemotherapy, surgery, autologous stem cell transplant, radiotherapy, immunotherapy, and differentiation therapy. Despite this multimodal approach, only approximately 50% of patients are cured of their disease (Yu et al., 2010).

The adoption of anti-GD2 antibodies has revolutionized the care of children with neuroblastoma. However, early trials of these antibodies largely demonstrated activity in bone marrow only disease and not in patients with bulky disease (Frost et al., 1997). The phase 3 trial of ch14.18 that resulted in FDA approval (dinutuximab) tested this antibody in a population of patients with no detectable disease (Yu et al., 2010). Multiple studies have demonstrated that GD2 antibody monotherapy does not mediate significant effect against established, bulk tumor. Therefore, there is an urgent need to enhance the potency of this agent. Recently, in a randomized control trial, the combination of dinutuximab with chemotherapy (irinotecan/temozolomide) was demonstrated to mediate objective responses in 53% of patients with recurrent neuroblastoma, compared to a 6% response rate in patients receiving irinotecan/temozolomide with temsirolimus (Mody et al., 2017). Thus, there is a clear potential to enhance the efficacy of this agent in neuroblastoma.

2.1.3 Osteosarcoma and Targeting GD2

Outcomes for patients with resectable, non-metastatic osteosarcoma have plateaued at approximately 70% using surgery plus multiagent chemotherapy. There is consensus that further progress against this disease requires the

development of targeted therapies that overcome resistance to standard cytotoxic agents. For patients who present with metastatic osteosarcoma or who have unresectable disease, outcomes are dismal with <20% survival and little progress has been made over the last several decades (Meyers & Gorlick, 1997). Similarly, patients with recurrent osteosarcoma have survival rates of approximately 20-30%, even after resection with or without chemotherapy (Meyers & Gorlick, 1997). There are few salvage therapies or options for experimental therapies for osteosarcoma.

We have found that 18/18 (100%) of osteosarcoma samples tested expressed GD2 with 15/18 (83%) expressed at high levels (Long et al., 2016). This stands in contrast to the other solid tumor histologies we studied, including Ewings sarcoma and rhabdomyosarcoma, where we observed nearly no staining on primary samples (2/15 for rhabdomyosarcoma; 7/35 for Ewings sarcoma). Similarly, a group at Memorial Sloan Kettering stained frozen osteosarcoma samples with their own validated anti-GD2 antibody (3F8) and found that 16/19 (84%) osteosarcomas expressed GD2, while only 2/18 (10%) of desmoplastic small round cell tumor samples were GD2 positive (Dobrenkov, Ostrovnaya, Gu, Cheung, & Cheung, 2016). Finally, an additional study found that at recurrence 31 of 32 samples (97%) from patients with osteosarcoma expressed GD2, the majority of which were expressed at high levels (Poon et al., 2015). The results demonstrate that the majority of osteosarcomas express GD2, in contrast to other sarcomas such as Ewing sarcoma and rhabdomyosarcoma. Anti-GD2 antibodies are currently in clinical trials for osteosarcoma (NCT02484443) and there have been several reported responses to anti-GD2 antibodies in this disease including a complete response to a monoclonal antibody and a PET response to a GD2xCD3 bispecific antibody (Frost et al., 1997), (Murray et al., 1994), (Yankelevich et al., 2019).

2.1.4 Targeting CD47 as a Macrophage Checkpoint

Macrophage phagocytosis of cells is regulated by a balance of inhibitory and activating receptors. CD47 is a cell surface protein that functions as a regulator of phagocytosis by cells of the innate immune system. CD47 binds the SIRP-alpha receptor on phagocytes, delivering an inhibitory signal (Jaiswal et al., 2009). In this way, CD47 functions as a "don't eat me" signal. Macrophages also recognize calreticulin, which is a pro-phagocytic or "eat me" signal expressed by cells slated for removal by the immune system (Chao, Alizadeh, et al., 2010).

Anti-CD47 antibodies bind CD47 and block its interaction with SIRP-alpha. This results in blockade of the "don't eat me" signal, pushing the macrophage balance towards phagocytosis and elimination of cancer cells. Most normal cells do not express calreticulin under normal conditions. Thus, even though CD47 is widely expressed, normal cells are largely unaffected by the CD47 antibody (Chao, Alizadeh, et al., 2010).

2.1.5 Targeting macrophage checkpoints in children

For cancers with high mutational burdens, such as melanoma, non-small cell lung cancer and colorectal cancers with microsatellite instability, blockade of PD-1, a T cell inhibitory signal, is often sufficient to unleash naturally acquired antitumor immunity (Gubin, Artyomov, Mardis, & Schreiber, 2015); (Rizvi et al., 2015). However, many pediatric cancers have a low mutational burden and are not sufficiently immunogenic to drive clinically significant antitumor immunity following checkpoint blockade. Sarcomas, in general, have relatively low mutational burdens and thus far responses to checkpoint blockade have been disappointing. Osteosarcoma, despite its deregulated genome, falls into the category of a cancer with an intermediate mutational burden and thus far, significant responses have not been observed following treatment with either ipilimumab (Merchant et al., 2016) or PD-1 blockade (K. L. Davis et al., 2020). Similarly, neuroblastoma manifests a relatively low number of genetic mutations (Pugh et al., 2013) and objective responses have not been observed following PD-1 blockade (R. J. Davis et al., 2017).

While single agent T cell checkpoint inhibition may not represent a successful therapeutic approach in pediatric cancer (K. L. Davis et al., 2020), other groups have focused on macrophages as immune effectors in pediatric cancers. Studies have demonstrated that pediatric cancers are heavily infiltrated by macrophages (Vakkila, Jaffe, Michelow, & Lotze, 2006). A recently published study demonstrated remarkable activity of Hu-5F9 in preclinical models of pediatric brain tumors

(Gholamin et al., 2017). Given the large numbers of macrophages that infiltrate sarcomas and neuroblastoma, this could represent a promising approach.

2.1.6 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 (J. Liu et al., 2015), (Huang, Ma, Gao, & Yao, 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 (X. Liu 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 (Liu, Kwon, Li, & Fu, 2017), (Huang et al., 2017).

Hu5F9-G4 (magrolimab) blocks the interaction of CD47 with its ligands and enables phagocytosis of human cancer cells (J. Liu 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 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 (J. Liu 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 (J. Liu 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, Alizadeh, et al., 2010), (Chao, Jaiswal, et al., 2010), (Chao, Majeti, & Weissman, 2011), (Krampitz et al., 2016), (Edris et al., 2012), (Gholamin et al., 2017), (Weiskopf 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, Alizadeh, et al., 2010), (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, Alizadeh, et al., 2010), (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), (J. Liu et al., 2015), (Sikic et al., 2019), (Willingham et al., 2012).

Mechanism of Action

Hu5F9-G4 (magrolimab) is an anti-CD47 monoclonal antibody that disrupts the CD47/SIRPα interaction to induce macrophage-mediated phagocytosis (J. Liu 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, Jaiswal, et al., 2010). Inhibiting CD47 signaling can also initiate an anti-tumor T-lymphocyte immune response and T-cell-

mediated killing (X. Liu et al., 2015).

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 (Angelo et al., 2014) 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 CL through the endogenous CD47 cellular sink.

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.

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 (Sikic et al., 2019) 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.

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 recommended phase 2 dose (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. 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.

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 cutaneous T-cell lymphoma (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 stable disease (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 objective response rate (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 duration of response (Willingham et al.) was not reached for either DLBCL or FL patients with a median follow-up of 13.8 and 21 months, respectively.

2.1.7 Dinutuximab

Dinutuximab is a mouse-human chimeric monoclonal IgG1 antibody recognizing the disialoganglioside (GD2), a cell surface glycolipid that is expressed on neuroblastoma cells and on normal cells of neuroectodermal origin, including the central nervous system and peripheral nerves. Dinutuximab binds to cell surface GD2 and induces cell lysis of GD2-expressing cells through antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

Dinutuximab in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid (RA) was approved by the FDA in March 2015 for treatment of high-risk neuroblastoma in pediatric patients who achieved at least a partial response to prior therapy. Dinutuximab's unique adverse event profile includes neuropathic pain and electrolyte abnormalities, as well as the usual monoclonal antibody events of infusion reactions, pain, pyrexia, and myelosuppression. Given the rare, yet severe peripheral sensory neuropathy that dinutuximab can elicit, the package insert contains black box labeling outlining the risk of neuropathy. Preclinical studies have demonstrated that the neuropathic pain associated with dinutuximab is mediated by GD2 binding on the nerve sheath surface.

Dinutuximab has been safely administered in combination with other standard therapies (Mody et al., 2017). COG sponsored a randomized trial to enhance the results of salvage chemotherapy for recurrent neuroblastoma which led to an increasingly frequent use of irinotecan and temozolomide and GM-CSF in combination with dinutuximab. A phase 1 trial (NCT01711554) combining ch14.18 with lenalidomide and 13-*cis*-RA is showing promising results in children and young adults with recurrent, refractory, or persistent neuroblastoma (Keyel & Reynolds, 2018).

2.2 Rationale for Combining GD2 and CD47 in Neuroblastoma and Osteosarcoma

Figure 3: Anti-GD2 and anti-CD47 antibodies result in synergistic activity and prolonged tumor clearance in xenograft models of neuroblastoma

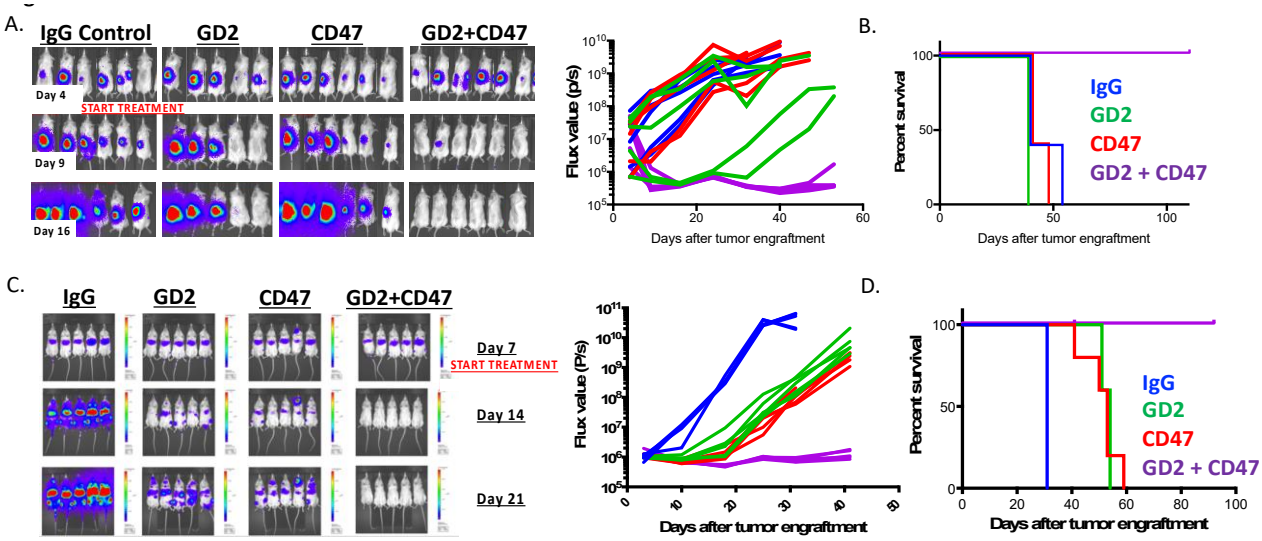

Figure 3: Anti-GD2 and anti-CD47 antibodies result in synergistic activity and prolonged tumor clearance in xenograft models of neuroblastoma. (A) KCNR was implanted into the kidney capsule of NSG mice prior to treating with anti-GD2, anti-CD47, or anti-GD2 and anti-CD47 antibodies. Tumor clearance was seen only in mice receiving anti-GD2 and anti-CD47, (B)resulting in prolonged survival. (C) NSG mice were intravenously injected with CHLA255 prior to treating with anti-GD2, anti-CD47, or anti-GD2 and anti-CD47 antibodies. Tumor clearance was only observed in mice receiving anti-GD2 and anti-CD47, (D) resulting in prolonged survival.

Given the success of anti-GD2 antibodies in neuroblastoma, we investigated whether these agents could synergize with CD47 blockade. Using localized and metastatic models of neuroblastoma, we found that combination of anti-GD2 and anti-CD47 antibodies led to tumor clearance and prolonged survival, while monotherapy had limited activity (**Figure 3A-D**). To assess the efficacy of this combination therapy in osteosarcoma, we used the MG63.3 cell line. Neither single agent anti-GD2 nor anti-CD47 had any effect on tumor growth kinetics in an orthotopic xenograft model, but the combination of the two agents prevented tumor growth and resulted in enhanced survival (

Figure 4A-B). Additionally, in a metastatic model of osteosarcoma that mimics the clinical situation of patients with pulmonary micrometastatic disease (

Figure 4C), the combination of anti-GD2 and anti-CD47 antibodies prevented the development of lung metastasis, while in all other groups, mice developed a high burden of metastatic disease (

Figure 4D). Further preclinical studies (data not shown) have demonstrated that GD2 itself may be a "Don't Eat Me" signal that inhibits macrophage phagocytosis and that GD2 crosslinking drives upregulation of calreticulin, marking tumor cells for removal by macrophages. Therefore, anti-GD2 and anti-CD47 antibodies are a rational combination that can result in significant anti-tumor activity in patients with neuroblastoma and osteosarcoma.

Figure 4: Anti-GD2 and anti-CD47 antibodies result in synergistic activity in xenograft models of osteosarcoma

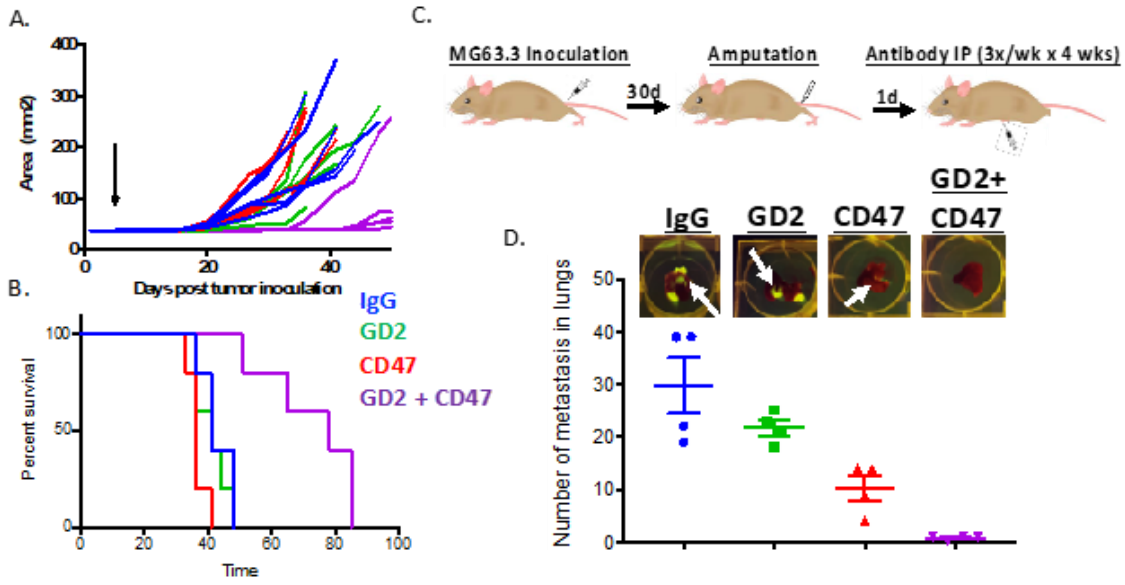

Figure 4: Anti-GD2 and anti-CD47 antibodies result in synergistic activity in xenograft models of osteosarcoma. (A) MG63.3 was implanted into the tibia of NSG mice three days prior to treating with anti-GD2, anti-CD47, or anti-GD2 and anti-CD47 antibodies. A delay in tumor growth was seen only in mice receiving anti-GD2 and anti-CD47 combined, (B) resulting in prolonged survival. (C) MG63.3 was implanted into the tibia of NSG mice. After four weeks, the primary tumor was amputated with the hind limb. Mice were treated with anti-GD2, anti-CD47, or anti-GD2 and anti-CD47 antibodies. (D) A reduction in the number and size of pulmonary metastasis was seen in mice in the combination group.

2.3 Correlative Studies Background

2.3.1 Explore biomarkers of response and resistance including genomic (CD47 expression, FcR polymorphisms and KiR phenotype) and immunologic (dinutuximab HACA, magrolimab ADA, peripheral immune subsets, and circulating cytokines)

CD47 expression is ubiquitous on most human tissues. It is currently unknown whether expression (qualitative or

quantitative) of CD47 on tumor cells or surrounding cells in the tumor microenvironment is predictive of response to CD47 blockade. CD47 expression will be assessed by immunohistochemistry using a validated antibody on tumor tissue, where available, including archival samples, tumor biopsy samples, and bone marrow samples (when involved by disease).

Genetic polymorphisms in the Fc Receptor (FcR) and Killer Cell Immunoglobulin-Like Receptor (KIR) phenotype have been associated with variable responses to antibody-based therapies, including anti-GD2 in neuroblastoma (Erbe et al., 2018; Siebert et al., 2016). Macrophage activity (as well as NK cell activity) are targets of anti-CD47 therapy, and these receptors may make a patient more or less likely to respond to anti-CD47 and/or anti-GD2.

As dinutuximab is a chimeric antibody consisting of murine variable regions fused to a human Fc region, some patients develop antibodies capable of recognizing and neutralizing dinutuximab (human anti-chimera antibodies, HACA). It is expected that many neuroblastoma patients on this trial will have been previously treated with dinutuximab. We will therefore measure baseline and on-treatment HACA as has been previously reported in the literature (Angelo et al., 2014).

Anti-CD47 can unleash the innate immune system through activation of macrophages and NK cells, but has also been shown to generate/unleash a native T cell response (Tseng et al., 2013). Therefore, patient blood and bone marrow (when obtained for disease evaluation) will be subjected to immune phenotyping to look for immune activation/response using validated CyTOF panels. Additionally, patient plasma will be collected during therapy to look for changes in circulating cytokines using the Luminex platform.

2.3.2 Explore biomarkers of response in the tumor microenvironment through MIBI on resected tissue or archival tissues including comparison of pre- and post- treatment tumor tissues from patients undergoing staged resection of pulmonary osteosarcoma

Despite frequent metastasectomy performed in osteosarcoma, there is a dearth of information on the immune microenvironment in lung metastases in osteosarcoma. By treating patients undergoing staged metastasectomy between the two resections, we will obtain pre- and post-treatment biopsies, which are rarely obtained on pediatric trials. This will allow us to compare the tumor immune microenvironment before and after treatment with anti-GD2/anti-CD47. We will evaluate these tumors using a validated Multiplexed ion beam imaging (MIBI) panel to explore the tumor immune microenvironment (Angelo et al., 2014).

3 PATIENT ELIGIBILITY

3.1 Eligibility Inclusion Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical or research record which will serve as the source document for verification at the time of audit.

3.1.1 Patients must have a history of histologically or cytologically confirmed NBL or osteosarcoma.

3.1.2 Diagnosis

Patients must have:

- Relapsed/Refractory High-Risk Neuroblastoma (NBL) (*defined as disease recurrence after completion of*

therapy, progressive disease on therapy, or refractory disease during induction therapy)

or

- Relapsed Osteosarcoma (*relapsed after frontline therapy and/or there must not be any potentially curative treatment options available at the time of enrollment)*

3.1.3 Disease Status

Patients must have measurable or evaluable disease as follows:

3.1.3.1 **Cohort B1:** Confirmed neuroblastoma: measurable NBL/ganglioneuroblastoma (defined as those lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with cross sectional imaging (CT scan or MRI), or ≥ 10 mm with calipers by clinical exam). Chest x-ray cannot be used to determine eligibility. Lesions must be MIBG positive, PET avid (if patient has a history MIBG negative disease) or biopsy proven NBL/ganglioneuroblastoma.

3.1.3.2 **Cohort B2:** Evaluable NBL (MIBG and/or bone marrow disease only)

3.1.3.3 **Cohort B3:** Measurable osteosarcoma (defined as those lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm (≥1 cm) with cross sectional imaging (CT scan, MRI, or calipers by clinical exam). Chest x-ray cannot be used to determine eligibility.

3.1.3.4 **Cohort B4:** Patients with relapsed resectable pulmonary osteosarcoma who are scheduled for a surgical resection.

Note: Subjects will not have measurable disease due to recently resected pulmonary metastases. Investigational therapy must begin within three weeks of resection. Staged resections are permissible; investigational therapy will be administered in between resections. Patients should receive one cycle of investigational therapy in between resections but can receive additional cycles to accommodate the most appropriate surgical schedule as determined by the treating physicians. Every effort will be made to have at least half of this cohort (five of ten patients) be those requiring a staged resection.

3.1.4 Prior Therapy:

- There is no limit to the number of prior treatment regimens. Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to initiation of study treatment. Acute toxicity of any previous therapy must have resolved to grade 1 or less or stabilized, unless specified elsewhere.
  - Myelosuppressive chemotherapy: Patients must not have received myelosuppressive chemotherapy within 3 weeks of initiation of study treatment (6 weeks if prior nitrosourea).
  - Hematopoietic growth factors: At least 7 days must have elapsed since the completion of therapy with a growth factor. At least 14 days must have elapsed after receiving pegfilgrastim.
  - At least 7 days must have elapsed since the completion of therapy with a biologic agent, targeted agent, tyrosine kinase inhibitor or a metronomic non-myelosuppressive regimen.
  - At least 4 weeks must have elapsed since prior therapy with ^{131}I-MIBG.
  - Monoclonal antibodies: At least 3 weeks must have elapsed since prior therapy that included a monoclonal antibody. Patients who have received prior therapy with GD2 antibodies, regardless of response to therapy, will be eligible.
  - At least 7 days must have elapsed since the last pharmacologic dose of systemic corticosteroids

3.1.5 Age:

- Arm A: Age ≥2 or < 18 years of age.
- Arm B: Age ≥2 or ≤ 35 years of age.

3.1.6 Performance Status: ECOG performance status ≤2; Subjects > 16 years of age: Karnofsky ≥ 50%; Subjects ≤ 16 years of age: Lansky scale ≥50% (see APPENDIX A: PERFORMANCE STATUS CRITERIA)

3.1.7 Patients must have adequate organ and marrow function as defined below: (supportive care is allowed per institutional standards, i.e., filgrastim, transfusion, etc.)

- absolute neutrophil count ≥ 1,000/mcL
- hemoglobin ≥ 9.5 g/dL, transfusion support acceptable
- platelets ≥ 100,000/mcL, independent of transfusions
- total bilirubin ≤ 1.5 X institutional upper limit of normal (ULN) for age (sum of conjugated and unconjugated)
- AST(SGOT)/ALT(SGPT) ≤ 5 × institutional ULN
- creatinine ≤ institutional ULN

OR

- glomerular filtration rate (GFR) ≥ 70 mL/min/1.73 m^2

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

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

3.1.10 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

3.1.11 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 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

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 enrollment and within 72 hours before the first administration of study treatment.

Note: Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential.

3.1.14 The effects of Hu5F9-G4 (magrolimab) monoclonal antibody on the developing human fetus are unknown and dinutuximab is known to be teratogenic. For this reason, female patients of childbearing potential must be willing to use one highly effective method of contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, during the study and continue for 4 months after the last dose of study treatment. 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.

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.

3.1.15 All patients and/or their parents or legally authorized representatives must have the ability to understand and the willingness to sign a written informed consent. Assent, where appropriate, will be obtained according to local institutional policy.

3.1.16 Cardiac Function: Cardiac ejection fraction ≥ 45% or shortening fraction ≥ 28%, no evidence of physiologically significant pericardial effusion as determined by an ECHO, MUGA or Cardiac MRI. No clinically significant ECG findings that in the judgment of the treating investigator would present a contraindication for treatment.

3.2 Exclusion Criteria

3.2.1 History of allergic reactions attributed to compounds of similar chemical or biologic composition to anti-GD2 monoclonal antibody (dinutuximab) or Hu5F9-G4 (magrolimab) monoclonal antibody or other agents used in this study.

3.2.2 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.3 Patients who are receiving any other investigational agents.

3.2.4 Pregnant women are excluded from this study because Hu5F9-G4 (magrolimab)is a monoclonal antibody on the developing human fetus are unknown and dinutuximab may cause fetal harm. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Hu5F9-G4 (magrolimab) or dinutuximab, breastfeeding should be discontinued if the mother is treated with Hu5F9-G4 (magrolimab) or dinutuximab.

3.2.5 Patients who have received prior treatment with CD47 or SIRPα-targeting agents.

3.2.6 Patients with red blood cell (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.

3.2.7 Patients with known inherited or acquired bleeding disorders are not eligible

3.2.8 Patients with prior hemolytic anemia or Evans Syndrome in the last 3 months.

3.2.9 Patients with significant medical diseases that would worsen the risk-benefit ratio of participating in this study. This includes but is not limited to acute myocardial infarction within the last 6 months, unstable angina, significant acute or chronic infections, or severely immunocompromised state.

3.2.10 Patients on the following medications at the time of study treatment initiation:

- Immunotherapy or immunosuppressive drugs (*e.g.* chemotherapy or systemic corticosteroids) EXCEPT for the following:
    - The only exception is for patients known to require 2 mg/kg or less of hydrocortisone (or an equivalent dose of an alternative corticosteroid) as premedication for blood product administration in order to

avoid allergic transfusion reactions. The use of conventional doses of inhaled steroids for the treatment of asthma is permitted, as is the use of physiologic doses of steroids for patients with known adrenal insufficiency.

- 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).

3.2.11 Patients administered a live vaccine within 28 days prior to initiation of study treatment.

3.2.12 Patients with active or previously treated central nervous system (CNS) metastasis.

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.

Females ages 2 to 35 years of age will be included in this study. Any other age is outside the scope of this study.

There is no discrimination for the inclusion and planned distribution of patients by gender, race, ethnicity for this study (see **Section 9.3**, Planned Enrollment Report).

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) 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). 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,

- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following documents outlined in Table 1:

Table 1: RCR Required Documentation

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

An active CTEP-IAM user account with a linked ID.me account (the latter required immediately for new CTEP-IAM accounts, and by July 1, 2023 for all users) is required to participate in the NCI clinical trials supported by the Cancer Trials Support Unit (CTSU) and to access all CTEP and CTSU websites and applications. In addition, 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, consenting, 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 CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

4.2 CTSU Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

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

4.2.1 IRB Approval

U.S. sites participating in the PEP-CTN network are required to use the NCI CIRB as of March 1, 2019. Local IRB review

will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the 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 emailing the email address above or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation,
- IRB-signed CTSU IRB Certification Form, and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site Principal Investigator (Site 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 to complete 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*)and 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 Form FDA 1572 in RCR profiles;
- Lists all sites on the IRB/REB approval as Practice Sites in Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

4.2.2 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;
- 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).

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review.

4.2.3 Submitting Regulatory Documents

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

To access the Regulatory Submission Portal, log in 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.

4.2.4 Delegation of Tasks Log (DTL)

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 describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List..

4.2.5 Checking Your Site's Registration Status

Site 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 sites 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.

Requirements For PEP-CTN Site Registration

IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification, and/or Protocol Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form

4.3 Patient Enrollment

Investigators should refer to the COG website to determine if the study is currently open for accrual.

4.3.1 OPEN

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in Oncology Patient Enrollment Network (OPEN).
Requirements for OPEN access:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created

CTEP-IAM accounts and by July 1, 2023 for all users);

- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization 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) must hold the 'OPEN Registrar' task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

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 at https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

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. Please 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.

4.3.2 Patient Registration

Prior to enrollment on study, patients must be assigned a COG patient ID number. This number is obtained via the COG Registry in the OPEN system once authorization for the release of protected health information (PHI) has been obtained.

If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.3.3 Reservation and Contact Requirements

Prior to enrolling a patient, a reservation must be made following the steps below and the Study Chair or Vice Chair notified. (The patient will need a COG patient ID number in order to obtain a reservation). Reservations may be obtained 24 hours a day through the Oncology Patient Enrollment Network (OPEN) system. Patients must be enrolled within 7 calendar days of making a reservation.

If the study is active, a reservation can be made by following the steps below:

1) Log in to https://open.ctsu.org/open/ using your CTEP IAM username and password.
2) In order to make a reservation, the patient must have an OPEN patient number. Click on the 'Slot Reservation' tab to create an OPEN patient number, under 'Patients'.
3) Using the OPEN patient number '**RESERVE**' a slot for that patient.

4) On the 'Create Slot Reservation' page, select the Protocol Number, enter the COG Patient ID, and choose the required stratum (if applicable) in order to obtain a reservation.

Refer to the 'Slot Reservation Site User Guide' posted under the 'Help' tab in OPEN for detailed instructions: https://www.ctsu.org/open/Site_Resources/Training/Users_Manual/CTSU-OPEN-SlotReservationSiteUserGuide.pdf

4.4 General Guidelines

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Patients who give informed consent for the protocol in order to undergo screening for eligibility are not considered enrolled and should not be enrolled until the screening is completed and they are determined to meet all eligibility criteria.

Following enrollment, patients should begin protocol treatment within 7 calendar days. Issues that would cause treatment delays should be discussed with the Study Chair. **Patients must not receive any protocol therapy prior to enrollment.**

4.4.1 Informed Consent/Assent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient or the patient's parents or guardian if the patient is a child. All patients and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines

4.4.2 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent. Documentation of the informed consent for screening will be maintained in the patient's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

4.4.3 Eligibility Checklist

Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist. A signed copy of the checklist will be uploaded into RAVE immediately following enrollment.

4.4.4 Institutional Pathology Report

Immediately following enrollment, the institutional pathology report for the diagnosis under which the patient is being enrolled must be uploaded into RAVE. The report must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission.

5 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Table 2: List of Biomarkers in Order of Priority

Note for participating sites: See Table 3 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 EET Biobank prior to testing.

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial (Integral, Integrated, or Exploratory) AND Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Tissue-based Biomarkers							
1	MIBI for immune cell infiltration	Multiplexed ion beam imaging CLIA: N No Review Required	Exploratory 1) Understand the baseline immune cell infiltration in archival samples of relapsed or refractory neuroblastoma and osteosarcoma 2) Compare the immune cell infiltration before and after treatment with anti-CD47/anti-GD2 in patients with relapsed pulmonary osteosarcoma undergoing staged resections 3) Compare the immune cell infiltration before and after treatment with anti CD47/anti-GD2 in patients with relapsed osteosarcoma or neuroblastoma undergoing optional biopsies	FFPE tumor tissue	1) Archival Tissue 2) Pulmonary Metastases resected from staged resection at enrollment and then after one cycle of protocol therapy (cohort B4 only) 3) Clinical biopsies obtained during therapy or at disease progression	1) Optional 2) Mandatory (cohort B4 only) 3) Optional	Angelo Laboratory, Department of Pathology, Stanford University Michael Angelo mangelo0@stanford.edu

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial (Integral, Integrated, or Exploratory) AND Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
2	CD47 Expression	Immunohistochemistry CLIA: N No Review Required	Exploratory Assess contribution of CD47 to disease response	Unstained slides from FFPE tumor tissue	1) Archival Tissue 2) Pulmonary Metastases resected from staged resection at enrollment and then after one cycle of protocol therapy (cohort B4 only) 3) Clinical biopsies obtained during therapy or at relapse	Optional	Stanford Pathology
3	Sample Banking		Sample banking for future study	Frozen tumor tissue (when available)	1) Available archival tissue 2) Pulmonary Metastases resected from staged resection at enrollment and then after one cycle of protocol therapy (cohort B4 only) 3) Clinical biopsies obtained during therapy or at disease progression	Optional	EET Biobank

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial (Integral, Integrated, or Exploratory) AND Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
4	CyTOF for immune subsets	Mass Cytometry CLIA: N	Exploratory To determine changes in the peripheral immune subsets as a result of treatment with anti-CD47 / anti-GD2	Mononuclear cells from bone marrow in Sodium Heparin tube	1) Baseline 2) Disease restaging (cycle 2, 4, 8, 12) 3) End of therapy	1) Mandatory (fresh or viably frozen) 2) Mandatory 3) Optional	Stanford Cancer Correlative Science Unit (CCSU) Bita Sahaf bsahaf@stanford.edu
5	Sample Banking		Sample banking for future study	Mononuclear cells and plasma from bone marrow in Sodium Heparin and EDTA tubes (Bilateral)	Baseline if available Disease restaging (cycle 2, 4, 8, 12) End of therapy	Optional	EET Biobank
Blood-based Biomarkers							
1	Magrolimab PK	ELISA CLIA: N No Review Required	Integrated Assess the drug concentrations achieved during this first in child trial	Serum from Red top tube	Safety lead-in D1, 8, 15 Cycle 1, D1, 8, 15, ARM B only: D22 Cycle 2, D1 Cycle 3, D1 Cycle 5, D1 Cycle 7, D1 Cycle 9, D1 Cycle 11, D1 End of therapy (all samples drawn prior to magrolimab infusion)	M (safety cohort and first three patients on any expansion cohorts)	PPD

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial (Integral, Integrated, or Exploratory) AND Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
2	Magrolimab anti-drug antibody (ADA) Testing	ECLIA CLIA: N No Review Required	Integrated Assess for immune responses against magrolimab	Serum from Red top tube	Safety lead-in D1 Cycle 1, D1 Cycle 2, D1 Cycle 3, D1 Cycle 5, D1 Cycle 7, D1 Cycle 9, D1 Cycle 11, D1 End of therapy (all samples drawn prior to magrolimab infusion)	M (safety cohort and first three patients on any expansion cohorts)	PPD
3	FcR receptor polymorphism	RT-PCR CLIA: N No Review Required	Exploratory Assess contribution of FcR polymorphisms to disease response	PBMC from EDTA tube	Baseline: Arm A: Safety Lead In-Week 1, D1 Arm B: Cycle 1, D1	Optional	Sondel Laboratory, University of Wisconsin) Paul Sondel pmsondel@humonc.wisc.edu
4	KiR phenotyping	RT-PCR CLIA: N No Review Required	Exploratory Assess contribution of KiR mismatching to disease response	PBMC from EDTA tube	Baseline: Arm A: Safety Lead In-Week 1, D1 Arm B: Cycle 1, D1	Optional	Sondel Laboratory, University of Wisconsin Paul Sondel pmsondel@humonc.wisc.edu

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial (Integral, Integrated, or Exploratory) AND Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
5	HACA antibody testing	ELISA CLIA: N No Review Required	Exploratory Assess contribution of Human anti- chimeric antibody response to disease response	Serum from Red top tube	ARM A: Cycle 1: Day 1, 5 ARM B: Cycle 1: Day 8, 12 Cycle 2: Day 1 and 5 Cycle 4: Day 1 and 5 End of therapy	Mandatory	Sondel Laboratory, University of Wisconsin Paul Sondel pmsondel@humonc.wisc.edu
6	Luminex for peripheral cytokines	Luminex CLIA: N No Review Required	Exploratory To assess for the presence of human cytokines	Plasma from blood in EDTA tube	Safety Lead-In and Cycles 1-2: Weekly prior to magrolimab infusion Subsequent cycles: Day 1 prior to infusion End of therapy	Mandatory	Stanford Human Immune Monitoring Center (HIMC) Holden Maecker maecker@stanford.edu
7	CyTOF for peripheral immune subsets	Mass Cytometry CLIA: N No Review Required	Exploratory To determine changes in the peripheral immune subsets as a result of treatment with anti-CD47/anti-GD2	Mononuclear cells from blood in Sodium Heparin tube	Safety Lead-In and Cycles 1-2: Weekly prior to magrolimab infusion Subsequent cycles: Day 1 End of therapy	Mandatory	Stanford Cancer Correlative Science Unit (CCSU) Bita Sahaf bsahaf@stanford.edu

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial (Integral, Integrated, or Exploratory) AND Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
8	Sample Banking		Sample banking for future studies	PBMCs from blood in EDTA	Safety Lead-In and Cycles 1-2: Weekly prior to magrolimab infusion Subsequent cycles: Day 1 prior to infusion End of therapy	Mandatory (bank cells when plasma is collected for cytokines)	EET Biobank

5.1 Exploratory/Ancillary Correlative Studies

5.1.1 MIBI for immune cell infiltration

Rationale: Tissue will be analyzed in an attempt to understand the baseline immune cell infiltration of relapsed or refractory neuroblastoma and osteosarcoma. If available, clinical biopsies or surgical samples obtained during treatment or at disease progression will be requested. Patients enrolled in cohort 4 undergoing staged pulmonary resections will have tissue obtained from the initial surgical resection, and then again from the second resection after completion of one cycle of Hu5F9-G4 (magrolimab) and dinutuximab.

Assay: Multiplexed ion beam imaging

Lab(s) Performing Correlative Study: Stanford

5.1.2 Hu5F9-G4 (magrolimab) Pharmacokinetics

Rationale: This blood-based biomarker will be mandatory in the patients participating in the safety cohort and in the first three patients enrolled in each of the expansion cohorts to assess the drug concentrations in the pediatric population.

Assay*: LC/MS*

Labs(s) Performing Correlative Study: PPD

5.1.3 Hu5F9-G4 (magrolimab) Anti-Drug Antibody (ADA)

Rationale: This blood-based biomarker will be mandatory in the patients participating in the safety cohort and in the first three patients enrolled in each of the expansion cohorts to assess development of anti-magrolimab antibodies.

Assay: ECLIA

Labs(s) Performing Correlative Study: PPD

5.1.4 FcR receptor polymorphism

Rationale: The purpose of this assay is to assess the contribution of KiR mismatching to disease response in patients with relapsed or refractory osteosarcoma and neuroblastoma.

Assay: Real-time PCR

Lab(s) Performing Correlative Study: University of Wisconsin, Laboratory of Paul Sondel, MD

5.1.5 HACA antibody testing

Rationale: The purpose of this assay is to assess the contribution of human anti-chimeric antibody response to disease response in patients with relapsed or refractory osteosarcoma and neuroblastoma.

Assay: ELISA

Lab(s) Performing Correlative Study: University of Wisconsin, Laboratory of Paul Sondel, MD

5.1.6 Peripheral Cytokine Assay

Rationale: The purpose of this assay is to assess the presence of human cytokine response to combination therapy of Hu5F9-G4 (magrolimab) and dinutuximab.

Assay: Luminex

Lab(s) Performing Correlative Study: Stanford HIMC

5.1.7 Peripheral Immune Subsets

Rationale: The purpose of this assay is to assess changes in the circulating immune subsets in response to combination therapy of Hu5F9-G4 (magrolimab) and dinutuximab.

Assay: CyTOF

Lab(s) Performing Correlative Study: Stanford CCSU

5.2 Processing and Storage of Specimens at EET Biobank

- **Processing of Tissue**
  Biopsies will be processed for FFPE blocks by the sites.

  Biopsies will be sectioned, and H&E stained for image scanning and histopathological examination by a designated pathologist. The H&E section will serve to confirm concordance with the institutional diagnosis and also estimate percent tumor content. An adequate biopsy sample will contain at least 50% tumor cells with minimal necrosis and stromal tissue.

  Processed samples will be stored at the EET Biobank as outlined below until they are ready to be sent for analyses as defined in the protocol.

- **Processing of Blood and Bone marrow**
  Upon receipt at the EET Biobank, fresh bone marrow in EDTA tubes and sodium heparin tubes as well as blood in EDTA tubes, sodium heparin tubes will be processed for mononuclear cells and plasma. Cells will be stored at 5 x 10^6 cells per vial in freezing media. At C1D1, 2 mL of blood in EDTA (of the 6 mL blood in EDTA received) will be extracted for DNA.

  Frozen serum will be accessioned and stored as listed below.

  Viably frozen bone marrow, processed locally per institutional SOPs, for mononuclear cells and plasma, will be accessioned and stored as listed below.

  Processed samples will be stored at the EET Biobank as outlined below until they are ready to be sent for analyses as defined in the protocol.

- **Storage of Specimens at EET Biobank**
  - Plasma and serum samples will be stored in a -80°C freezer
  - PBMCs will be stored in a vapor phase of liquid nitrogen (LN_2) freezer
  - FFPE tissue blocks will be stored at ambient temperature
  - Snap-frozen tissue will be stored in a LN_2 vapor phase freezer

5.3 Summary Table for Specimen Collection

Tumor Tissue Specimens at Baseline and As Available While on Study:

Archival tumor tissue slides or block will be requested upon enrollment to the study as outlined in Table 3 below. In addition, clinical biopsies or surgical samples obtained during treatment or at disease progression will be requested, if available as outlined in Table 3 below.

Table 3: Summary Table for Specimen Collection

Time Point	Specimen	Specimen Shipment
Archival [1]		
	• Archival Tissue: Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred) **OR** • 1 H&E stained slide (3-5 µm) **AND,** • 35-55 unstained, uncharged, air-dried slides (10 µm)	EET Biobank
	• Archival tumor tissue: Snap frozen tumor tissue	
On Study Biopsy (Any clinical biopsies while on study) [1, 3]		
	• Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred) **OR** • 1 H&E stained slide (3-5 µm) **AND,** • 35-55 unstained, uncharged, air-dried slides (10 µm)	EET Biobank
	• Snap frozen tumor tissue	
Cohort B4 (Tissue from metastasectomy at enrollment) [1]		
	• Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred) (from multiple metastases, if present) **OR** • 1 H&E stained slide (3-5 µm) (from multiple metastases, if present) **AND,** • 35-55 unstained, uncharged, air-dried slides (10 µm) (from multiple metastases, if present)	EET Biobank

	• Snap frozen tumor tissue (from multiple metastases, if present)	
Arm A: Safety Lead-In Day 1 (Week 1) (Prior to dosing)		
	• 5mL bone marrow[2, 4] in a green top (Sodium Heparin) tube	EET Biobank
	• 5mL bone marrow[2, 4] in a purple top (EDTA) tube	
	• 2mL blood in a purple top (EDTA) tube	
	• 4mL blood in a purple top (EDTA) tube	
	• 5mL blood in a green top (Sodium Heparin) tube	
	• 3mL blood in a red top (serum) tube	PPD
	• 3mL blood in a red top (serum) tube	
ARM A: Safety Lead-In Day 8 (Week 2)		
	• 3mL blood in a red top (serum) tube	PPD
	• 4mL blood in a purple top (EDTA) tube	EET Biobank
	• 5mL blood in a green top (Sodium Heparin) tube	
ARM A: Safety Lead-In, Day 15 (Week 3)		
	• 3mL blood in a red top (serum) tube	PPD
	• 4mL blood in a purple top (EDTA) tube	EET Biobank
	• 5mL blood in a green top (Sodium Heparin) tube	
Arm B: Priming, Week 1, Day 1 (Prior to dosing)		
	• 5mL bone marrow[4] in a green top (Sodium Heparin) tube	EET Biobank
	• 5mL bone marrow[4] in a purple top (EDTA) tube	
	• 2mL blood in a purple top (EDTA) tube	
	• 4mL in a purple top (EDTA) tube	
	• 5mL blood in a green top (Sodium Heparin) tube	
	• 3mL blood in a red top (serum) tube	PPD
	• 3mL blood in a red top (serum) tube	

ARM A: Cycle 1: Week 1, Day 1 ***ARM B: Cycle 1: Week 2, Day 8***		
	• 3mL blood in a red top (serum) tube	PPD
	• 4mL blood in a purple top (EDTA) tube	EET Biobank
	• 5mL blood in a green top (Sodium Heparin) tube	
Draw *prior to* dinutuximab infusion	• 2mL blood in a red top tube, processed for serum and frozen[5]	
ARM A: Cycle 1 Week 1, Day 5 ***ARM B: Cycle 1 Week 2, Day 12***		
Draw immediately *after* dinutuximab infusion	• 2mL blood in a red top tube processed for serum and frozen[5]	EET Biobank
ARM A: Cycle 1 Week 2, Day 8 ***ARM B: Cycle 1 Week 3, Day 15***		
	• 3mL blood in a red top (serum) tube	PPD
	• 4mL blood in a purple top (EDTA) tube	EET Biobank
	• 5mL blood in a green top (Sodium Heparin) tube	
ARM A: Cycle 1 Week 3, Day 15 ***ARM B: Cycle 1 Week 4, Day 22***		
	• 3mL blood in a red top (serum) tube	PPD
	• 4mL blood in a purple top (EDTA) tube	EET Biobank
	• 5mL blood in a green top (Sodium Heparin) tube	
Cohort B4 (Tissue from metastasectomy after Cycle 1)[1]		
	• Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred) (from multiple metastases, if present) **OR** • 1 H&E stained slide (3-5 µm) (from multiple metastases, if present) • 35-55 unstained, uncharged, air-dried slides (10 µm) (from multiple metastases, if present)	EET Biobank
	• Snap frozen tumor tissue (from multiple metastases, if present)	
Cycle 2 Day 1		

	• 3mL blood in a red top (serum) tube	PPD
	• 3mL blood in a red top (serum) tube	PPD
	• 4mL blood in a purple top (EDTA) tube	EET Biobank
	• 5mL blood in a green top (Sodium Heparin) tube	
Draw *prior to* dinutuximab infusion	• 2mL blood in a red top tube, processed for serum and frozen[5]	
Cycle 2 Day 5		
Draw *after* dinutuximab infusion	• 2mL blood in a red top (serum) tube[5]	EET Biobank
Cycle 2 Day 8		
	• 4mL blood in a purple top (EDTA) tube	EET Biobank
	• 5mL blood in a green top (Sodium Heparin) tube	
Cycle 2 Day 15		
	• 4mL blood in a purple top (EDTA) tube	EET Biobank
	• 5mLblood in a green top (Sodium Heparin) tube	
End of Cycle 2 and all restaging (Cycle 4, 8, and 12)		
	• 5mL bone marrow[2] in a green top (sodium heparin) tube	EET Biobank
	• 5mL bone marrow[2] in a purple top (EDTA) tube	
Cycle 3, 5, 7, 9, 11 Day 1		
	• 3mL blood in a red top (serum) tube	PPD
	• 3mL blood in a red top (serum) tube	PPD
Cycle 3-12 Day 1		
	• 4 mL blood in a purple top (EDTA) tube	EET Biobank
	• 5mL blood in a green top (Sodium Heparin) tube	
Cycle 4 Day 1		
Draw *prior to* dinutuximab infusion	• 2mL blood in a red top tube, processed for serum and frozen[5]	EET Biobank
Cycle 4 Day 5		

Draw *after* dinutuximab infusion	• 2mL blood in a red top (serum) tube[5]	EET Biobank
End of Therapy or Progression		
	• 3mL blood in a red top (serum) tube	PPD
	• 3mL blood in a red top (serum) tube	PPD
	• 2mL blood in a red top tube, processed for serum and frozen	EET Biobank
	• Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred)[1, 3] **OR** • 1 H&E stained slide (3-5 µm) • 35-55 unstained, uncharged, air-dried slides (10 µm)	
	• Snap frozen tumor tissue[1, 3]	
	• 5mL bone marrow[2] in a green top (sodium heparin) tube	
	• 5mL bone marrow[2] in a purple top (EDTA) tube	
	• 4mL blood in a purple top (EDTA) tube	
	• 5mL blood in a green top (Sodium Heparin) tube	

[1] For all 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 – 56).

[2] For bone marrow aspirate or biopsy, the corresponding bone marrow report must be submitted uploaded to Rave and sent with the specimen to the EET Biobank.

[3] Two (2) core biopsies will be used for FFPE and three (3) additional cores will be snap-frozen. Each core biopsy must be embedded in a separate block. See details in section 5.6.2.

[4] Fresh **or** viably frozen bone marrow aspirate can be accepted prior to the Priming dose (Week 1, Day 1). Fresh bone marrow aspirate must be collected and shipped to the EET Biobank following patient enrollment in OPEN, and prior to the Priming dose (Week 1, Day 1). If available, frozen bone marrow aspirate collected within 4 weeks (28 days) of the Priming dose (Week 1, Day 1) can be provided to the EET Biobank instead of fresh bone marrow.

[5] Specimen can be stored in the refrigerator if Dinutuximab infusion ends at a time where specimen processing is not possible (Friday night or over the weekend). Processing should be done no more than 3 days following collection.

5.4 Specimen Procurement Kits and Scheduling

5.4.1 Specimen Procurement Kits

Kits for the collection and shipment of specimens frozen tissue 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 *PED-CITN-03* protocol to request a kit. Please note that PED-CITN-03 may include more than one type of kit. Each user may order two kit types 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 and in the instructions included with the kits.

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

5.4.1.1 Scheduling of Specimen Collections

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

- Tumor tissue specimens collected during biopsy procedures for clinical indications will be fixed in formalin and embedded prior to shipment. These tissues can be collected on any day.
- Specimens submitted frozen 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.
- Fresh blood or bone marrow specimens may be collected and shipped Monday through Friday.

5.5 Specimen Labeling

Blood and Bone Marrow Aspirate Specimen Labels

Include the following on blood and bone marrow aspirate specimens (including whole blood or bone marrow and frozen, processed blood or bone marrow products – like serum, plasma, and mononuclear cells):

- Study ID
- COG Patient ID Number (a unique patient identification number assigned via the COG Registry in the OPEN system at registration)
- Timepoint
- Specimen type (e.g., Blood, serum, bone marrow, plasma, mononuclear cells)
- Laterality (R for right or L for left), if bone marrow (to be added by hand)
- Collection date and time (to be added by hand)

Tissue Specimen Labels

Include the following on all tissue specimens or containers (e.g., cryovial or block):

- Study ID
- COG Patient ID Number
- Timepoint
- Specimen type (*e.g.*, formalin-fixed paraffin-embedded [FFPE] Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Tissue type (P for primary, M for metastatic or N for normal)
- Surgical pathology ID (SPID) number (when applicable)
- Block number from the corresponding pathology report (if available)
- Collection date (to be added by hand)
- Slide section number (only if tissue is submitted as slides) *(*to be added by hand)

5.6 Specimen Collection

5.6.1 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
- FFPE tumor tissue block(s) must be submitted. The optimal block is at least 50% 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)
- Thirty-five to fifty-five (35 – 55) 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 5.5 for labeling instructions.

5.6.2 FFPE and Frozen Tumor Biopsies

- **Biopsy Specimen Collection Procedure (does not apply to metastasectomy)**

  - Core biopsies at least 1 cm in length will be obtained through Interventional Radiology by a percutaneous approach using a 16-18-gauge needle. Only percutaneous biopsies will be performed on patients with solid tumors. However, excisional biopsy or endoscopic biopsy is allowed if medically indicated and can be used for analysis.
  - Two (2) core biopsies will be used for FFPE and three (3) additional cores will be snap-frozen. If tissue is limited, equally divide samples between FFPE and snap-frozen.
  - If fine needle aspiration (FNA) is available, especially for sampling of bone lesions in order to assure specimen adequacy and to avoid specimen decalcification, use of FNA before core needle biopsy is preferred. Real-time cytopathologic immediate evaluation of the FNA specimen can confirm that the chosen target area of a lesion is satisfactory for obtaining the core needle biopsy specimens. If real-time cytopathology assessment of FNA specimens is not available, collection of FNA specimens prior to core needle biopsy procurement is recommended. FNA specimens are not an acceptable substitute for tissue biopsy cores; do not submit to the EET Biobank.
  - For pathologic examination of removed tissue, place a portion of the biopsy specimen in a labeled specimen container with fixative for transport to your Pathology Department. (This specimen container is not provided in the shipping kit.) The pathology report must be uploaded to Medidata Rave as soon as available.
  - These instructions also apply to additional specimens from medically necessary surgical procedures performed for clinical care.

- **Formalin Fixation of Tissue**

- Tissue must be fixed in formalin for 12-24 hours and each core biopsy must be embedded in a separate block. Embedding must be completed within 72 hours of adding 70% ethanol to tissue. Sites must use automated tissue processors and not use microwave tissue processors. Sites should follow embedding protocols where the total processing time from 70% ethanol to block embedding exceeds 4 hours. Tissue fixed in formalin for 24-36 hours prior to embedding should be shipped but will be recorded as non-compliant.
- Neutral-buffered formalin must be used as fixative (no acid-based products).
- The optimal block is at least 70% tumor. Specimen size requirements are as follows:
  - Surface area: 25 mm^2 optimal (minimum 5 mm^2)
  - Volume: 1 mm^3 optimal (minimum 0.2 mm^3)

5.6.3 Blood and Bone Marrow Sample Collection Procedures

- **Collection in EDTA Purple-Top Tubes**

1. Label EDTA tube(s) according to instructions in Section 5.5.2.
2. Collect blood in EDTA Purple-Top tube(s) and gently invert 5-10 times to mix.
3. Maintain specimens at ambient temperature (room temperature) during collection and transport.
4. Ship on day of collection (*whenever possible*) to the EET Biobank according to instructions in Section 5.7.

- **Collection in Sodium Heparin Green-Top Tubes**

1. Label sodium heparin tube(s) according to instructions in Section 5.5.2.
2. Collect blood in sodium heparin tubes and gently invert 5-10 times to mix.
3. Maintain specimens at ambient temperature (room temperature) during collection and transport.
4. Ship on day of collection (*whenever possible*) to the EET Biobank according to instructions in Section 5.7.

- **Collection in Red Top Serum Tubes for the EET Biobank**

1. Label Red Top Serum (RTS) tube according to instructions in Section 5.5.2.
2. Collect 2 mL of whole blood using a Red Top Serum (RTS) tube. Invert the collection tube 8 – 10 times (gently) to facilitate the clotting process.
3. Allow blood to clot upright at room temperature for at least 30 minutes (maximum 60 minutes) prior to processing. If the blood is not immediately processed after the clotting period, then tubes should be stored (after the 30-60 minutes of clotting time) at 4°C for no longer than 4 hours. Process serum from red top tubes by centrifuging for 10 minutes at 1,200 × g at room temperature.
4. Using a clean transfer pipette, aliquot serum into the labeled (using the label printed from the ETCTN Specimen Tracking System or following the instructions in Section 5.4.2) cryovials at an aliquot volume of 1 mL per tube. Avoid picking up red blood cells when aliquoting by keeping the pipet above the red blood cell layer and leaving a small amount of serum in the tube. Tightly secure the cap of the vials before storage. Aliquoting and freezing of serum specimens should be completed within 1 hour of centrifugation.
5. Store serum cryovials upright in a specimen box or rack in an -70°C to -90°C or colder freezer prior to shipping to the EET Biobank. Do not allow specimens to thaw after freezing.
6. Ship on day of collection (*whenever possible*) to the EET Biobank according to instructions in Section 5.7.

- **Collection in Red Top Serum Tubes for Hu5F9-G4 PK testing (PPD)**

1. Label Red Top Serum (RTS) tube according to instructions in Section 5.5.2.
2. Collect 3 mL of whole blood using a Red Top Serum (RTS) tube. Invert the collection tube 8 – 10 times (gently) to facilitate the clotting process.

Note: Serum should be physically separated from contact with the cells soon as possible with a maximum time limit

of 1 hour from the time of collection.

3. Centrifuge Red Top Serum (RTS) tubes(s) for 10 minutes at 1,000-1,300 RCF (g) in a swing bucket centrifuge (15 minutes using a fixed-angle centrifuge).
4. Using a plastic transfer pipette, transfer equal aliquots (~ 0.4 mL) of the serum layer to the corresponding cryovials. **In the event you do not yield enough serum for 4 equal aliquots (~0.4 mL), fill the first 3 aliquots with 0.4 mL of serum first. Then fill the remaining cryovials equally with the remaining serum.**
5. Allow enough space between the serum and tube caps to account for expansion during freezing. Do not overfill. Cap the cryovial and place immediately upright on ice.
6. Freeze immediately at -70° C until shipment.
7. Ship frozen to PPD weekly if possible. Otherwise, ship to PPD day of collection.

- **Collection in Red Top Serum (RTS) tubes for Magrolimab anti-drug antibody (ADA) testing (PPD)**

1. Label Red Top Serum (RTS) tube according to instructions in Section 5.5.2.
2. Collect 3 mL of whole blood using a Red Top Serum (RTS) tube. Invert the collection tube 8 – 10 times (gently) to facilitate the clotting process.

   Note: Serum should be physically separated from contact with the cells soon as possible with a maximum time limit of 1 hour from the time of collection.

3. Centrifuge Red Top Serum (RTS) tubes(s) for 10 minutes at 1,000-1,300 RCF (g) in a swing bucket centrifuge (15 minutes using a fixed-angle centrifuge).
4. Using a plastic transfer pipette, transfer equal aliquots (~ 0.4 mL) of the serum layer to the corresponding cryovials. **In the event you do not yield enough serum for 4 equal aliquots (~0.4 mL), fill the first 3 aliquots with 0.4 mL of serum first. Then fill the remaining cryovials equally with the remaining serum.**
5. Allow enough space between the serum and tube caps to account for expansion during freezing. Do not overfill. Cap the cryovial and place immediately upright on ice.
6. Freeze immediately at -70° C until shipment.
7. Ship frozen to PPD weekly if possible. Otherwise, ship to PPD day of collection.

5.7 Shipping Specimens from Clinical Sites to the EET Biobank

5.7.1 General Shipping Information

When kits are provided, the shipping container sent with kit contents should be used to ship specimens.

For **all tissue,** the corresponding pathology report is required.

- Tissue embedded in paraffin may be batched and shipped Monday through Thursday.
- Frozen specimens (tissue, serum, bone marrow) may be shipped Monday through Thursday.
- Fresh blood and Bone marrow must be shipped overnight on the same day as collection for arrival on Tuesday through Saturday at the EET Biobank. Saturday delivery is only available for shipments of fresh blood or bone marrow.
- The date and time of collection and shipping date must be entered into the ETCTN STS for all submitted specimens.

- Do not ship specimens the day before a U.S. federal holiday. If you are unsure whether the EET Biobank will be able to receive specimens, then please contact the EET Biobank.

5.7.2 Additional Shipping Information

Shipping of FFPE Blocks and Glass Slides Using Supplies Provided by the Institution

1. Before packaging blocks or slides, verify that each specimen is labeled according to Section 5.4.2.
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.
6. Ship specimens to the address listed below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

Shipping Blood or Bone Marrow Using Supplies Provided by the Institution

1. Before packaging specimens, verify that each specimen is labeled according to the instructions in 5.4.2.
2. Place the collection tubes into zip-lock bags.
3. Next, place specimens 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 packaged collection tube(s) and a copy of the shipping manifest from the Sample Tracking System 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.

Shipping Frozen Serum Using Supplies Provided by the Institution

1. Before packaging specimens, verify that each specimen is labeled according to the instructions in 5.4.2 and the lids of all primary receptables 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 in the insulated shipping container with dry ice. Layer the bottom of the compartment 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 shipping 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 lid of 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.

Shipping Frozen Tissue in a Single-Chamber Kit

1. Before packaging specimens, verify that each specimen is labeled according to the instructions in 5.4.2.
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 the 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 in the kit compartment with dry ice. Layer the bottom of the compartment 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 compartment 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 kit chamber.
7. Place the Styrofoam lid on top to secure specimens during shipment. Do not tape the inner chamber shut.
8. Close the outer lid of the Specimen Procurement Kit and tape it shut with durable sealing tape. Do not completely seal the container.
9. Complete a FedEx air bill and attach to top of shipping container.
10. Complete a dry ice label.
11. Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
12. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.7.3 Required Forms for Specimen Submissions

Sample label data should be entered into the specimen transmittal forms in RAVE for tumor tissue and bone marrow samples. Sample label data for blood should be recorded on the sample worksheets, which must accompany the sample shipments and be uploaded to RAVE. See below for required forms.

	Required Forms
Tissue	1.Specimen transmittal forms in RAVE 2.Corresponding Pathology Report
Bone Marrow Aspirate	1.Specimen transmittal forms in RAVE 2.Corresponding Bone Marrow Report (once available)
Blood or Serum	See the following appendices: Appendix G: Pharmacokinetic Worksheet for Magrolimab, Arm A Appendix H: Pharmacokinetic Worksheet for Magrolimab, Arm B Appendix I: Anti-Drug Antibody (ADA) Worksheet for

	Magrolimab Appendix J: FcR Receptor for Polymorphism Worksheet for Arm A Appendix K: FcR Receptor for Polymorphism Worksheet for Arm B Appendix L: KiR Phenotyping Worksheet for Arm A Appendix M : KiR Phenotyping Worksheet for Arm B Appendix N: Human Anti-Chimera Antibodies (HACA) Testing Worksheet Arm A Appendix O: Human Anti-Chimera Antibodies (HACA) Testing Worksheet Arm B Appendix P: Luminex for Peripheral Cytokines Worksheet for Arm A Appendix Q: Luminex for Peripheral Cytokines Worksheet for Arm B Appendix R: CyTOF for Peripheral Immune Subsets Worksheet for Arm A Appendix S: CyTOF for Peripheral Immune Subsets Worksheet for Arm B Appendix T: Sample Banking Worksheet for Arm A Appendix U: Sample Banking Worksheet for Arm B Appendix V: Central Monitoring Plan

5.7.4 Shipping address

Ship specimens to the address below using overnight courier, early morning delivery option:

EET Biobank Nationwide Children's Hospital
700 Children's Dr., WA1340
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred.

Please see the FedEx Account Usage Guidelines Memo here

- Contact Information for Assistance

For all queries, please use the contact information below:

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

5.8 Shipping Specimens from Clinical Sites to Specific Laboratories

5.8.1 Shipping Hu5F9-G4 PK Test Specimens to PPD

Standard procedures for packing specimens should be used (*e.g.,* cryopreserved blood samples). Priority Overnight shipping is required for all specimens.

Ship samples to the following:

ATTN: LiMajor Pittman
PPD
2246 Dabney Road
Richmond, VA 23230
Phone: 804.977.8459

5.8.2 Shipping Hu5F9-G4 (Magrolimab) ADA to PPD

Standard procedures for packing specimens should be used (*e.g.,* cryopreserved blood samples). Priority Overnight shipping is required for all specimens.

Ship samples to the following:

ATTN: LiMajor Pittman
PPD
2246 Dabney Road
Richmond, VA 23230
Phone: 804.977.8459

6 TREATMENT AND IMAGING PLAN

This is a phase 1 trial dose finding trial with Hu5F9-G4 (magrolimab) a recombinant humanized IgG4 monoclonal antibody, given in combination with dinutuximab (Unituxin®), a GD2-binding monoclonal antibody for children and young adults with relapsed/refractory (R/R) NB and relapsed osteosarcoma. The first cohort of patients will receive a Safety Lead-In of single agent Hu5F9-G4 (magrolimab) at Dose Level 1 (30 mg/kg) followed by Hu5F9-G4 (magrolimab) in combination with dinutuximab as described in **Section 6.1.1**. Once the safe dose of the combination is established, patients will be enrolled to one of four expansion cohorts who receive the combination of Hu5F9-G4 (magrolimab) at the recommended phase 2 dose (RP2D) and a fixed dose of dinutuximab as outlined in **Section 6.4**.

Treatment will be administered on both an inpatient and outpatient basis. Dinutuximab is administered inpatient, while Hu5F9-G4 (magrolimab) can be given 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.

The *Study Calendars* in **Section 11** outline the timing of procedures and visits.

6.1 Agent Dose and Administration

All patients, regardless of whether they are enrolled on the "single agent Safety Lead-In" Dose Finding Cohort (Arm A) or the Expansion Cohorts (Arm B), will receive a priming dose of Hu5F9-G4 (magrolimab) (1 mg/kg) intravenous (IV) on Day 1 of week 1 (see **Figure 1** and **Figure 2**).

6.1.1 Dose Finding Cohort (Arm A)

There will be two evaluations for dose limiting toxicity (DLT) conducted on this study in Arm A (see **Figure 1** and **Figure 2**).

6.1.1.1 Safety Assessment During "single agent Safety Lead-In"

Patients aged ≥2 or < 18 years of age will be enrolled on the "single agent Safety Lead-In", and will receive a therapeutic dose of Hu5F9-G4 (magrolimab) (30 mg/kg IV) on Day 1 of weeks 2 and 3 for a 21-day "single agent Safety Lead-In" cycle (see **Figure 1** and **Figure 2**). An assessment for DLTs as defined in **Section 6.3** will be performed during and at the end of the 21-day "single agent Safety Lead-In".

Any patient who does not develop DLT during the "single agent Safety Lead-In" may proceed to Cycle 1 (combination therapy with Hu5F9-G4 (magrolimab) plus dinutuximab) and will be evaluable for safety assessment during and after Cycle 1. When dinutuximab is administered immediately after Hu5F9-G4 (magrolimab), redosing with acetaminophen and diphenhydramine is not necessary. The intravenous line should be flushed well between drug administrations.

Patient enrollment and start of treatment during the safety "single agent Safety Lead-In" assessment will be staggered by 7 days for each patient enrolled. Three patients will initially be enrolled at Dose Level 1 (30 mg/kg IV).

- If 0 of the initial 3 patients develops a DLT during the 21-day "single agent Safety Lead-In", the next phase of safety will be evaluated in Cycle 1 as outlined below (**Section 6.1.1.2**).
- If 1 of the initial 3 patients develops a DLT (**Section 6.3**) during the 21-day "single agent Safety Lead-In", then an additional 3 patients will be enrolled at Dose Level 1.
    - If 0 of these 3 additional patients (totaling 1/6) develops a DLT during the 21-day "single agent Safety Lead-In", the study will continue to evaluate DLTs in Cycle 1 as outlined below (**Section 6.1.1.2**).
    - If ≥1 of these 3 additional patients (totaling 2/6) develop a DLT, the dose of Hu5F9-G4 (magrolimab) will be de-escalated to Dose Level -1 (20 mg/kg) during weeks 2 and 3 in the next 3 patients. The safety of Dose Level -1 will be similarly evaluated in 3-6 patients.
- If ≥ 2 of the initial 3 patients develop a DLT during the 21-day "single agent Safety Lead-In", the dose of Hu5F9-G4 (magrolimab) will be de-escalated to Dose Level -1 (20 mg/kg) during weeks 2 and 3, in the next 3 patients. The safety of Dose Level -1 will be similarly evaluated in 3-6 patients.
- If ≥ 2 patients develop DLT during the "single agent Safety Lead-In" using Dose Level -1, enrollment will pause pending discussions with the sponsor, IRB and FDA.

Any patient who develops a DLT during the "single agent Safety Lead-In" will be removed from additional therapy on this study.

6.1.1.2 Safety Assessment During Cycle 1

An assessment for DLTs will be performed during and at the end of the 21 days of Cycle 1 (**Figure 2**). In the absence of

DLTs or progressive disease (PD), patients may proceed to a maximum of 12 cycles of combination therapy. After Cycle 2, each subsequent cycle will consist of Hu5F9-G4 (magrolimab) administered on Day 1 of weeks 1 and 3 of the cycle (week 2 will be a week of rest), with dinutuximab administration on Day 2 through 5 of week 1.

The initial dosing of each patient during Cycle 1 safety assessment will be staggered by 7 days for each patient. Three weeks (21 days) must elapse after completion of Cycle 1 in the final patient in the dose finding cohort (Arm A) to allow for safety assessment before treating additional patients at the determined recommended phase 2 dose (RP2D) in Arm B.

The following rules apply to the DLT assessment conducted at the conclusion of Cycle 1 (week 6).

If Dose Level 1 is selected as safe for Cycle 1 based on safety results from the 'Single agent Safety Lead-In', three patients will be enrolled, and the following applies:

- If 0 of the initial 3 patients develops a DLT during Cycle 1, the study will proceed to the expansion cohorts (Arm B) (see **Section 6.4**).
- If 1 of the initial 3 patients develops a DLT during Cycle 1, then an additional 3 patients will be enrolled at Dose Level 1.
    - If 0 of these 3 additional patients (totaling 1/6) develops a DLT during Cycle 1, the study will proceed to the expansion cohorts (Arm B) (see **Section 6.4**).
    - If ≥ 1 of these 3 additional patients (totaling ≥ 2/6) develop a DLT during Cycle 1, an additional 3 patients will be enrolled to receive the priming dose followed by Hu5F9-G4 (magrolimab) de-escalated to Dose Level -1 (20 mg/kg) during Cycle 1 (Table 4). The safety of Dose Level -1 will be similarly evaluated in 3-6 patients.
    - If 2 of the initial 3 patients develop a DLT during Cycle 1, an additional 3 patients will be enrolled to receive the priming dose followed by Hu5F9-G4 (magrolimab) de-escalated to Dose Level -1 (20 mg/kg) during Cycle 1. The safety of Dose Level -1 will be similarly evaluated in 3-6 patients.

Table 4: Doses for Hu5F9-G4 (magrolimab) and Dinutuximab during Dose Finding Cohort (Cycle 1)

Dose Level	Dose of Hu5F9-G4 (magrolimab)	Dose of Dinutuximab
Level -1	20 mg/kg IV	17.5 mg/m^2 IV
Level 1	30 mg/kg IV	17.5 mg/m^2 IV

The dose level of Hu5F9-G4 (magrolimab) that is deemed safe during both the 'Single agent Safety Lead-In' and Cycle 1 in the dose finding cohort (Arm A) will be used to evaluate safety in the Arm B schedule. The first three (3) patients enrolled to Arm B will be evaluated for DLT, and three weeks (21 days) must elapse after completion of Cycle 1 in the final patient to allow for safety assessment before treating additional patients in Arm B to confirm the recommended phase 2 dose (RP2D) (Arm B) (see **Section 6.2.1.2**). These three patients will be allocated and analyzed in their respective cohorts for efficacy analysis.
If protocol therapy is delayed (due to re-scheduling for administrative reasons or temporary suspension due to toxicity), disease evaluations and correlative exploratory biology studies will follow the originally scheduled calendar dates and should *not* be adjusted for the dose delay. The results of these evaluations and assays while on treatment should reflect the effect of the former dose(s), not the current/prospective clinical status at the time of drug administration. All clinical assessments and laboratory tests (and their respective windows) will adjust with the dose delay to reflect the patient's clinical

status at the time of drug administration.

The *Study Calendars* in **Section 11** outline the timing of procedures and visits for Arm A and Arm B.

6.2 Regimen Description and Supportive Care Guidelines

6.2.1 Hu5F9-G4 (Magrolimab) and Dinutuximab (Unituxin®) Agent Administration

6.2.1.1 Dose Finding Cohort (Arm A) Regimen

Table 5: Regimen Description for Dose Finding Cohort (Arm A)

Agent	*Premedications; Precautions*	*Dose*	*Route*	*Schedule*	*Cycle Length*
Hu5F9-G4 (magrolimab)	Administer according to guidelines in **Section 6.2.1.3**. Acetaminophen oral (PO) and diphenhydramine (IV) or a comparable regimen up to 15 minutes before the first two doses of Hu5F9-G4 (magrolimab), and in case of re-priming of the patient after > 4 weeks interruption in treatment. Monitor for infusion reactions during and for 1-hour post infusion during the priming dose. Any patients experience AEs during this period should be monitored as clinically indicates for up to 24 hours post infusion. Treatment of infusion reactions will be as clinically indicated.	10 mg/kg (max 650 mg) of acetaminophen; 0.5 - 1 mg/ kg (max 50 mg) of diphenhydramine^	Acetaminophen PO; Diphenhydramine IV	Priming: Day 1, Week 1	21 days (3 weeks)
		Priming: Hu5F9-G4 (magrolimab) - 1 mg/kg	Priming: Infuse IV (peripheral or central line) over 3 hours (± 30 min)		
		"Single Agent Safety Lead-In": Hu5F9-G4 (magrolimab) 30 mg/kg*	Subsequent infusions: Infuse IV over 2 hours (± 10 min)	"Single Agent Safety Lead-In": Day 1, Weeks 2 and 3	
		Cycles 1 and subsequent cycles: Hu5F9-G4 (magrolimab) 30 mg/kg*		Cycle 1: Day 1, Weeks 1, 2 and 3 Cycle 2: Day 1 Weeks 1, 2 and 3 Cycle 3 and subsequent cycles: Day 1 of Weeks 1 and 3 of each cycle (Week 2 is skipped)**	
Dinutuximab	Administration requires premedication	10 mg/kg (max 650 mg) of acetaminophen; 0.5	Acetaminophen PO Diphenhydramin	Cycles 1 (Week 1): Days 2-5;	

	(acetaminophen - oral, diphenhydramine - IV, and analgesia) and hydration prior to initiation according to **Section 6.2.1.4** Administer 0.9% Sodium Chloride Injection USP 10 mL/kg as an IV over 1 hour prior to initiating drug infusion	- 1 mg/ kg (max 50 mg) of diphenhydramine^ Analgesia per section 6.2.1.4 Dinutuximab - 17.5 mg/m^2	e^ IV (no need to be repeated if dinutuximab immediate follows previous drug infusion) Analgesia as described below in **Section 6.2.1.4**. Dinutuximab in 100 mL bag of 0.9% Sodium Chloride Injection USP (mix by gentle inversion - DO NOT shake)	Cycle 2 (Week 1): Days 2-5; Subsequent cycles: Days 2-5 of the first week of each subsequent cycle	
* Dose will be de-escalated to 20 mg/kg if 2 or more patients develop DLT during the "Single Agent Safety Lead-In" or Cycle 1. ** Cycles may be repeated as long as the patient does not have unacceptable toxicity (see **Section 6.3** or **Section** Error! Reference source not found.) or disease progression to a maximum of 12 cycles ^ Hydroxyzine (0.5-1 mg/kg, Max dose 50 mg) PO may substitute for diphenhydramine					

6.2.1.2 Expansion Cohorts (Arm B) Regimen

Once the RP2D is determined from the dose finding cohort, 4 expansion cohorts will be enrolled on Arm B on this study as defined in **Section 6.4**. Expansion cohorts B1-B3 will receive a priming dose of Hu5F9-G4 (magrolimab) (1 mg/kg) on week 1, followed in week 2 with Hu5F9-G4 (magrolimab) administered at RP2D on Day 1 and dinutuximab 17.5 mg/m^2 on Days 2-5. Hu5F9-G4 (magrolimab) will be administered at RP2D on Day 1 of week 3 and 4. A maximum of 12 cycles (see Table 6) can be completed in the absence of DLT or disease progression.

Patients in Arm B Cohort B4 will be enrolled in two subgroups:

1. Those who are scheduled for resection of lung lesion(s) (preferred), or those who have recently undergone resection of lung lesion(s) will start the Hu5F9-G4 (magrolimab)/dinutuximab within four weeks of resection as outlined in **Section 6.4** and Table 6, and
2. Those who are scheduled for resection of lung lesions in a stepwise fashion. Patients in this group will initiate treatment between resections as described in **Section 6.4**. Prior to resection all patients will receive the Hu5F9-G4 (magrolimab)/dinutuximab as outlined in Table 6. If restart of Hu5F9-G4 (magrolimab)/dinutuximab occurs within four (4) weeks of the last dose of Hu5F9-G4 (magrolimab), the patient will pick up the regimen as per the next scheduled regimen cycle for a maximum of 5 cycles postoperatively.
   If the restart of the Hu5F9-G4 (magrolimab)/dinutuximab is delayed beyond four weeks of the last dose of Hu5F9-G4 (magrolimab), the post-surgical regimen will be conducted as per Table 7and will require a re-priming dose of Hu59-G4 (magrolimab).

Every attempt will be made to enroll to the "step-wise resection" subgroup prior to the first resection in order to obtain tissue from the resection for research correlatives. If subjects are enrolled after the initial resection, a request will be made

for archived tissue for analysis. Within 4 weeks after the initial resection, patients will receive the priming dose of Hu5F9-G4 (magrolimab) on Day 1, followed by Cycle 1 in week 2 with Hu5F9-G4 (magrolimab) administered at RP2D on Day 1 and dinutuximab 17.5 mg/m^2 on Days 2-5, followed by Hu5F9-G4 (magrolimab) at RP2D on Day 1 of weeks 3 and 4 until the second resection (see Table 6 below). Upon recovery from the second resection, the cycles may be repeated to a maximum of 5 cycles (adjuvant therapy). If the cycles are restarted within 4 weeks of the last dose of Hu5F9-G4 (magrolimab), the patient will pick up the regimen as per the next scheduled regimen cycle as per Table 6. If restarting the regimen is delayed beyond 4 weeks of the last dose of Hu5F9-G4 (magrolimab), the patient will restart as per Table 7 and will require a re-priming dose of Hu59-G4 (magrolimab) with repeat of cycle 1 and 2 with weekly dosing of Hu5F9-G4 (magrolimab).

Table 6: Regimen Description for Arm B - Expansion Cohorts B1 – B3 (Confirmed Neuroblastoma, Evaluable Neuroblastoma, Measurable Osteosarcoma), **Cohort B4** (Resectable, pulmonary only relapsed osteosarcoma**) **- Non-staged resections and Cohort B4 – Staged resections prior to surgery and post resection with restart within 4 weeks of last dose**

Agent	*Premedications; Precautions*	*Dose*	*Route*	*Schedule*	*Cycle Length*
Hu5F9-G4 (magrolimab)	Administer according to guidelines in **Section 6.2.1.3**. Acetaminophen oral (PO) and diphenhydramine (IV) or a comparable regimen up to 15 minutes before the first two doses of Hu5F9-G4 (magrolimab), and in case of re-priming of the patient after > 4 weeks interruption in treatment. Monitor for infusion reactions during and for 1-hour post infusion during the priming dose. Any patients experience AEs during this period should be monitored as clinically indicates for up to 24 hours post infusion. Treatment of infusion reactions will be according to standard operating procedures.	10 mg/kg (max 650 mg) of acetaminophen ; 0.5 - 1 mg/kg (max 50 mg) of diphenhydramine^	Acetaminophen PO; Diphenhydramine IV	Priming: Day 1 Week 1	21 days (3 weeks)
		Priming: Hu5F9-G4 (magrolimab) 1 mg/kg	Priming: Infuse IV (peripheral or central line) over 3 hours (± 30 min)		
		Cycles 1-2: Hu5F9-G4 (magrolimab) RP2D mg/kg*	Subsequent infusions: Infuse IV over 2 hours (± 10 min)	Cycle 1: Day 1, Weeks 2, 3 and 4 Cycle 2: Day 1, Weeks 1, 2 and 3 Cycle 3 and subsequent cycles: Day 1 of Weeks 1 and 3 of each cycle (Week 2 is skipped)**	
Dinutuximab	Administration requires premedication (acetaminophen - oral, diphenydramine -IV, and analgesia) and hydration prior to initiation according	10 mg/kg (max 650 mg) of acetaminophen ; 0.5 - 1 mg/ kg (max 50 mg) of diphenhydrami	Acetaminophen PO Diphenhydramine^ IV (no need to be repeated if dinutuximab	Cycles 1 (Week 2): Days 2-5 Subsequent cycles: Days	

	to **Section 6.2.1.4** Administer 0.9% Sodium Chloride Injection USP 10 mL/kg as an IV over 1 hour prior to initiating drug infusion	ne^ Analgesia per section 6.2.1.4 Dinutuximab - 17.5 mg/m^2	immediate follows previous drug infusion) Analgesia as described below in **Section 6.2.1.4**. Dinutuximab in 100 mL bag of 0.9% Sodium Chloride Injection USP (mix by gentle inversion- DO NOT shake)	2-5 of the first week of each subsequent cycle	
* Determined during dose finding cohort. ** Cycles may be repeated as long as the patient does not have unacceptable toxicity (see **Section 6.3** or **Section** Error! Reference source not found.) or disease progression to a maximum of 12 cycles (in Cohorts B1 through B3) or to a maximum of 5 cycles post resection (Cohort B4) ^ Hydroxyzine (0.5-1 mg/kg, Max dose 50 mg) PO may substitute for diphenhydramine					

Table 7: Regimen Description for Arm B - Expansion Cohort B4 Staged Resection – Post Resection with Delayed Restart > 4 weeks (Resectable, pulmonary only relapsed osteosarcoma**)

Post-Surgical resection for staged bilateral pulmonary metastases (regimen for at least 1 cycle prior to pulmonary metastesectomy) if restart delayed					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Hu5F9-G4 (magrolimab)	Administer according to guidelines in **Section 6.2.1.3**. Acetaminophen oral (PO) and diphenhydramine (IV) or a comparable regimen up to 15 minutes before the first two doses of Hu5F9-G4 (magrolimab). Monitor for infusion reactions during and for 1-hour post infusion during the priming dose. Any patients experience AEs during this period should be monitored as clinically indicates for up to 24 hours post infusion. Treatment of infusion reactions will be	10 mg/kg (max 650 mg) of acetaminophen; 0.5 - 1 mg/ kg (max 50 mg) of diphenhydramine^	Acetaminophen PO; Diphenhydramine IV	Post resection Priming: Day 1, Week 1	21 days (3 weeks)
		Post resection Priming: Hu5F9-G4 (magrolimab) - 1 mg/kg	Priming: Infuse IV (peripheral or central line) over 3 hours (± 30 min)		
		Post resection Cycles 1-2: Hu5F9-G4 (magrolimab) RP2D mg/kg*	Subsequent infusions: Infuse IV over 2 hours (± 10 min)	Post resection Cycle 1: Day 1, Weeks 2, 3 and 4 Post resection Cycle 2: Day 1 of each week	

	according to standard operating procedures.			Post resection Cycle 3 and subsequent cycles: Day 1 of Weeks 1 and 3 of each cycle (Week 2 is skipped)	
Dinutuximab	Administration requires premedication (acetaminophen - oral, diphenydramine -IV, and analgesia) and hydration prior to initiation according to **Section 6.2.1.4** Administer 0.9% Sodium Chloride Injection USP 10 mL/kg as an IV over 1 hour prior to initiating drug infusion	10 mg/kg (max 650 mg) of acetaminophen; 0.5 - 1 mg/ kg (max 50 mg) of diphenhydramine^ Analgesia per section 6.2.1.4 Dinutuximab - 17.5 mg/m^2	Acetaminophen PO Diphenhydramine^ IV (no need to be repeated if dinutuximab immediate follows previous drug infusion) Analgesia as described below in **Section 6.2.1.4**. Dinutuximab in 100 mL bag of 0.9% Sodium Chloride Injection USP (mix by gentle inversion- DO NOT shake)	Post resection Cycles 1 (Week 2): Days 2-5; Subsequent Post resection cycles: Days 2-5 of the first week of each subsequent cycle	

* Determined during dose finding cohort.
** Patients who are scheduled for resection of lung lesion(s) unilateral or those who have recently undergone resection of lung lesion may continue the regimen for up to 5 cycles post resection in the absence of unacceptable toxicity or disease progression/recurrence.
^ Hydroxyzine (0.5-1 mg/kg, Max dose 50 mg) PO may substitute for diphenhydramine

6.2.1.3 Clinical Care for Administration of Hu5F9-G4 (magrolimab)

A priming dose of Hu5F9-G4 (magrolimab) is required on week 1, prior to starting therapy and upon restart of therapy if > four weeks occurs since the last dose of Hu5F9-G4 (magrolimab). The priming dose (1 mg/kg) will be infused over 3 hours (+/- 30 minutes) via a peripheral or central line. Protecting IV bag from light is not required. In-line IV filter set is not required. Subsequent IV doses can be infused over 2 hours (+/- 10 minutes)**.** If Hu5F9-G4 (magrolimab) dosing is ever delayed for greater than 4 weeks, a re-priming dose must be administered on week one, with scheduled dosing restarted 1 week later as depicted in **Figure 2**.

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

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. Refer to section 7.2.4 for assessments to be performed and resulted prior to the administration of the priming dose.

Anemia is a known and well described risk for Hu5F9-G4, which can occur in early doses and is transient.

- Within 24 hours prior to the Priming dose (Week 1) of Hu5F9-G4 (magrolimab) infusion, all patients must have a documented hemoglobin level of ≥ 9.5 g/dL, per eligibility criterion 3.1.7.
- Within 24 hours prior to the first full dose (Week 2) of Hu5F9-G4 (magrolimab) infusion, all patients must have a documented hemoglobin level of ≥ 9.0 g/dL.
- Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet the minimum hemoglobin threshold, as noted above, prior to administrating each of the first 2 doses of Hu5F9-G4 (magrolimab).
- An additional hemoglobin must be checked 3 to 6 hours after the initiation of the first (Priming) and second (Week 2) 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 of complications of anemia.

Men and women of reproductive potential must use effective contraception while receiving study treatment and for 4 months after the last dose of Hu5F9-G4 (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 **Section 6.8** of for further details.

Since infusion reactions can occur, all patients should be monitored pre-priming dose (within 30 minutes), every 30 minutes (±10) during priming dose infusion, for 1-hour post-infusion of the priming dose with vital signs (heart rate, respiratory rate, blood pressure, temperature, pulse oximetry) or as clinically indicated. Vital signs and AEs will be collected 30 (±10) minutes and 1 hour (±10 minutes) post-infusion. 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 with hourly (±20 minutes) vital signs during and for 1-hour (±20 minutes) post-infusion for Cycle 1. Further doses (Cycle 2+) do not require post-infusion observation, but hourly (±20 minutes) vital signs during the infusion. Patients who experience any treatment-related AEs during the observation period should be further monitored as clinically appropriate.

6.2.1.4 Clinical Care for Administration Dinutuximab (Unituxin®)

Dinutuximab will be administered inpatient; ensure that cardiopulmonary resuscitation medications and equipment are available. Administer required premedication and hydration prior to initiation. Administer dose over 10-20 hours at an infusion rate initially at 0.875 mg/m^2/hour for 30 minutes, or as per institutional guidelines. Infusion rates may be gradually increased as tolerated to a maximum rate of 1.75 mg/m^2/hour, or as per institutional guidelines. The infusion duration may be extended up to 20 hours for anticipated toxicities (pain, fever, tachycardia, tachypnea, hypotension), not responding to other supportive measures, and the duration used should be recorded. The maximum infusion time is 20 hours; dinutuximab administration must be stopped after 20 hours even if the total dose has not been administered. The total dose given in 20 hours should be recorded.

- Analgesics for pain management

Administer analgesia and opioids as per institutional guidelines. As recommended, morphine sulfate (50 mcg/kg) should be

administered intravenously immediately prior to initiation of dinutuximab and then continue as a morphine sulfate drip at an infusion rate of 20 to 50 mcg/kg/hour titrated to effect during and for two hours following completion of dinutuximab, as per institutional guidelines.

Administer additional 25 mcg/kg to 50 mcg/kg intravenous doses of morphine sulfate as needed for pain up to once every 2 hours followed by an increase in the morphine sulfate infusion rate in clinically stable patients, or as per institutional guidelines.

Consider using fentanyl or hydromorphone if morphine sulfate is not tolerated, as per institutional guidelines.

If pain is inadequately managed with opioids or to reduce opiate requirements during dinutuximab therapy, consider use of gabapentin or lidocaine in conjunction with intravenous morphine or as per institutional guidelines.

To optimize the effect of gabapentin, it should be initiated 1 week prior to expected start of antibody so that it can be increased to full dose by the start of dinutuximab administration. Dosing should follow institutional standards; however, the following dosing may be considered:

- Day 1: 5 mg/kg/dose (max 300 mg/dose) at bedtime
- Day 2: 5 mg/kg/dose (max 300 mg/dose) BID
- Day 3: 5 mg/kg/dose (max 300 mg/dose) TID – patients should be at this dose by the time of admission for cycle 1 dinutuximab
- Gabapentin doses can be increased further if necessary; institutional guidelines should be followed.

Lidocaine dosing should follow institutional standards; however, the following dosing may be considered:

- Initiate continuous infusion at 1 mg/kg/hour (bolus) with the continuous infusion rate of is 0.5 -2 mg/kg/hour.
- Lidocaine levels should initially be checked every 8 hours (Q8h) but may be spaced out once therapeutic concentrations have been achieved. Dose should be titrated in 25% increments to achieve therapeutic serum concentrations (goal 2-4 mcg/mL).
- Consider dose reduction in patients with hepatic disease.

- Premedications for infusion reactions

  - Antihistamines and Antipyretics

Administer an antihistamine such as diphenhydramine (0.5 to 1 mg/kg; maximum dose 50 mg) intravenously over 10 to 15 minutes starting 20 minutes prior to initiation of dinutuximab and as tolerated every 4 to 6 hours during the dinutuximab infusion, as per institutional guidelines.

  - Acetaminophen

Administer acetaminophen (10 to 15 mg/kg/dose; maximum dose 650 mg) PO approximately 20 minutes prior to each dinutuximab infusion and every 4 to 6 hours as needed for fever or pain, or as per institutional guidelines.

  - Ibuprofen

Administer ibuprofen (5 to 10 mg/kg/dose) every 6 hours as needed for control of persistent fever or pain, as per institutional guidelines.

- Monitoring Procedures

Vital signs (heart rate, respiratory rate, blood pressure, temperature, pulse oximetry) will be collected prior to the beginning of dinutuximab infusion (within 30 minutes) and every 30 (±10) minutes for the first hour of infusion, and then hourly during infusion, or as clinically indicated. Post-infusion, vital signs and AEs will be collected every 30 (±10) minutes twice, then hourly (±20) minutes for a total of 4 hours. For patients who previously tolerated the study agent without infusion-related reactions, the post-infusion monitoring period may be reduced at the discretion of and documented by the treating physician.

Document intake and output on the day of dinutuximab administration.

Standard imaging will be performed for disease assessment where indicated and according to the protocol schedule (screening, disease assessment at the conclusion of Cycle 2 and 4 and then every 4 cycles) (see **Section 11**).

6.3 Definition of Dose-Limiting Toxicity

Adverse events that occur within the first 21 days of the 'single agent Lead-In' dosing of Hu5F9-G4 (magrolimab) or during the 21 days of Cycle 1 during the combination Hu5F9-G4 (magrolimab) and dinutuximab drug infusions, are ***at least possibly related*** to at least 1 study agent, and are **≥ *Grade 3 in severity*** will be considered DLTs with the following additional criteria or exceptions:

Hematologic Toxicity:

- Anemia is an expected toxicity of Hu5F9-G4 (magrolimab) and dinutuximab, especially in patients who have had extensive prior therapy with chemotherapy, and therefore anemia and a need for blood transfusions will not be considered a DLT. Grade 3 hemolytic anemia that is medically significant, requires hospitalization or prolongation of existing hospitalization, is disabling, or limits self-care activities of daily life (ADLs) will be considered a DLT.

- Thrombocytopenia can be expected in this heavily pretreated population who have had extensive prior therapy with chemotherapy, and therefore platelet count decreased in the absence of hemorrhage will not be considered a DLT unless < 25,000/mcL for > 14 days despite supportive care.

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

Non-hematological Toxicity:

- Any Grade 3 or greater, non-hematological toxicity will be considered a DLT with the following *exceptions*:

  a. Pain and sensory neuropathy are expected toxicities of dinutuximab, but pain or sensory neuropathy at levels described in Table 8**: Adverse Reactions Requiring Permanent Discontinuation of Dinutuximab** will be considered a DLT. Pain requiring sedation and respiratory support for control will also be considered a DLT.
  b. Tumor lysis syndrome, including associated abnormalities (e.g., electrolytes, uric acid, renal function).
  c. Grade 3 low electrolyte levels that are correctable and asymptomatic.
  d. Grade 3 hypoalbuminemia. Such individuals should receive supplementation as indicated. Hypocalcemia toxicity grade should be assigned based on the calcium level corrected for degree of hypoalbuminemia according to the following formula: for every albumin decrease of 1 gm/dL a total calcium increase of 0.2 mmol/L is to be made.
  e. Grade 3 transaminase, alkaline phosphatase, bilirubin or other liver function test elevation, provided there is resolution to ≤ grade 2 with supportive care within 7 days and is not associated with other clinically

significant consequences. Grade 3 transaminase elevation, alkaline phosphatase or hyperbilirubinemia elevation of any duration in patients with liver involvement due to tumor will not be considered a DLT, although Grade 4 hepatic toxicity will be considered DLT.

f. 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.

g. Grade 3 fatigue that resolves to ≤Grade 2 within 1 week.

h. Grade 3 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.

i. Grade 3 or 4 infection or neutropenic fever although Grade 4 infection uncontrolled for > 7 days will be considered DLT.

j. Grade 3 electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia, etc.) that resolves to ≤Grade 2 or baseline within 1 week. Grade 4 hyponatremia not responsive to appropriate fluid management for dinutuximab will be considered a DLT.

k. 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.

l. Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.

m. Grade 3 decrease in vision that resolves to grade 1 or better before the next dose dinutuximab will not be considered a DLT and dose will be modified as per Section 7.3.2. Eye disorders such as sluggish light reflex or other visual disturbances that do not cause visual loss will not be considered DLT. Subtotal or total vision loss will be considered a DLT.

n. Capillary leak syndrome and/or hypotension (grade 3-4) which resolves to ≤Grade 2 or baseline within 8 hours with maximum supportive care.

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

6.4 Dose Expansion Cohorts

Upon determining RP2D, enrollment to 4 expansion cohorts will proceed to evaluate evidence of clinical activity (cohorts B1-3) and safety/feasibility of using this combination drug approach after surgery (cohort B4) (Figure 2).

Cohort B1 – Confirmed neuroblastoma: measurable neuroblastoma/ganglioneuroblastoma
Cohort B2 – Evaluable neuroblastoma
Cohort B3 – Measurable osteosarcoma
Cohort B4 – Resectable, pulmonary only relapsed osteosarcoma

All subjects will receive the priming dose of 1 mg/kg Hu5F9-G4 (magrolimab) on Day 1 of week 1. On Day 1 of week 2, subjects will receive Hu5F9-G4 (magrolimab) at RP2D followed by 17.5 mg/m^2 dinutuximab IV on Days 2-5. Then, they will receive Hu5F9-G4 (magrolimab) at RP2D on Day 1 of week 3 and week 4 (**Figure 2** and **Section 6.2.1.2**).

Cycle 2 will consist of Hu5F9-G4 (magrolimab) at RP2D on Day 1 of week 1 in combination with 17.5 mg/m^2 dinutuximab IV given on Days 2-5, followed by Hu5F9-G4 (magrolimab) at RP2D on Day 1 of weeks 2-3 (see **Figure 2** and **Section 6.2.1.2**). A disease evaluation will be conducted after Cycle 2 and Cycle 4, and then after every 4 cycles (every 12 weeks) until progressive disease or a maximum of 12 cycles (except cohort four which will have a maximum of five cycles after the patient is rendered No Evidence of Disease (NED)). After Cycle 2, each subsequent cycle will consist of Hu5F9-G4

(magrolimab) administered on Day 1 of weeks 1 and 3 of the cycle (week 2 will be a week of rest), with dinutuximab administration on Day 2-5 of week 1.

Cohort B4 will consist of some patients who will undergo a unilateral thoracotomy for removal of metastatic lesions which will render them NED. Those patients will begin therapy when deemed safe by clinical judgement of the treating physician/surgeon. These patients will receive the priming dose of 1 mg/kg Hu5F9-G4 (magrolimab) on Day 1 of week 1, followed by Hu5F9-G4 (magrolimab) at RP2D on Day 1 of week 2 in combination with 17.5 mg/m^2 dinutuximab IV given on Days 2-5, followed by Hu5F9-G4 (magrolimab) at RP2D on Day 1 of weeks 3-4 for Cycle 1 (see **Figure 2** and **Section 6.2.1.2**). Cycle 2 will consist of Hu5F9-G4 (magrolimab) at RP2D on Day 1 of week 1 in combination with 17.5 mg/m^2 dinutuximab IV given on Days 2-5, followed by Hu5F9-G4 (magrolimab) at RP2D on Day 1 of weeks 2-3 (see **Figure 2**). A disease evaluation will be carried out after 2 cycles and then after 5 cycles until progressive/recurrent disease. After Cycle 2, Hu5F9-G4 (magrolimab) will be administered at RP2D on Day 1 of weeks 1 and 3 of cycles 3 – 5 (week 2 will be a week of rest) with dinutuximab administration on Day 2-5 of week 1 in each cycle. Patients on Cohort B4 will receive a maximum of five cycles after the patient is rendered NED.

Cohort B4 will also consist of other patients scheduled for staged thoracotomy who will receive the Priming Dose and Cycle 1 within 4 weeks after the initial resection of pulmonary disease. Upon completion, as per previously scheduled, the patient will undergo the second thoracotomy, and subsequently resume Cycle 2 of Hu5F9-G4 (magrolimab)/dinutuximab when deemed safe by clinical judgement of the treating physician. Cycle 2 will consist of Hu5F9-G4 (magrolimab) at RP2D on Day 1 of week 5 in combination with 17.5 mg/m^2 dinutuximab IV given on Days 2-5, followed by Hu5F9-G4 (magrolimab) at RP2D on Day 1 of weeks 2-3 (see **Figure 2**). A disease evaluation will be carried out after 2 cycles (i.e., end of Cycle 3) and then after 5 cycles (i.e., end of Cycle 6) until recurrent disease (see Section 12). After Cycle 2 in the post-surgical regimen, Hu5F9-G4 (magrolimab) will be administered at RP2D on Day 1 of weeks 1 and 3 of cycles 3 – 5 (2nd week will be a week of rest) with dinutuximab administration on Days 2-5 of week 1 in each cycle. Patients on Cohort B4 may receive a maximum of five cycles after their second surgical resection.

Doses of Hu5F9-G4 (magrolimab) and dinutuximab in the expansion cohorts may be interrupted, delayed or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed. Both Hu5F9-G4 (magrolimab) and dinutuximab must be delayed at the same time. Protocol therapy must be discontinued for dose delays greater than 14 days except for reasons outlined in **Section 6.6**. In such cases, the Protocol Principal Investigator must be consulted prior to resuming treatment.

For the expansion cohorts, patients will continue to be monitored for occurrence of DLT during Cycle 1. If 2 of the first 5 patients or if ≥2 of 6 patients experience DLT, the Principal Investigator will discuss with all study investigators and with CTEP whether further addition of patients is needed to re-assess the RP2D.

Monitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the Principal Investigator when a DLT has occurred.

6.5 Criteria for Removal from Protocol Therapy and Off Study Criteria

6.5.1 Criteria for Removal from Protocol Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for to a maximum of 12 cycles (9 months of combination therapy) [except in cohort B4, resectable, pulmonary only relapsed osteosarcoma, who may continue combination therapy for a total of 5 cycles after pulmonary resection] or until one of the following criteria applies:

- Disease progression

- Intercurrent illness that prevents further administration of treatment.
- Unacceptable adverse event(s), including, but not limited to, any one of the following:
  - Patients who have Grade 4 infusions reactions occurring with the first dose of Hu5F9-G4 (magrolimab) or dinutuximab will be permanently discontinued from treatment.
  - Patients who receive Hu5F9-G4 (magrolimab) premedication with corticosteroids and still have a Grade 3 or 4 infusion reaction on subsequent doses will generally be permanently discontinued from treatment, unless continued therapy is approved by the Study PI, Site PI and Sponsor.
  - Patients who receive dinutuximab and experience any of the AEs listed in Table 8**: Adverse Reactions Requiring Permanent Discontinuation of Dinutuximab**
    or recur after appropriate management as outlined in Section 7.3.2.
- Patient who develops a DLT during the "single agent Safety Lead-In" will be removed from additional therapy on this 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 of disease
- Patient non-compliance
- Pregnancy
  - All women of childbearing 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(s) can no longer provide the study agents.

6.5.2 Off Study Criteria

a) Thirty days after the last dose of the investigational agent for patients who develop disease progression during combination therapy.
b) The fifth anniversary of the date the patient was enrolled on this study, or until disease progression, for patients who complete the maximum number of cycles or who met off protocol therapy criteria in Section 6.5.1 other than disease progression.
c) Withdrawal of consent for any required observations or data submission.
d) The patient does not receive protocol treatment after study enrollment.
e) Patient enrollment onto another COG study with therapeutic (anti-cancer) intent.
f) Lost to follow-up.
g) Death

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

6.6 Duration of Follow-Up

Patients who complete the maximum number of cycles or who met off-therapy criteria other than disease progression will be asked to participate in study follow-up and be evaluated at month 2 (± 1 week), month 4 (± 2 weeks), month 6 (± 4 weeks), month 9 (± 4 weeks), and month 12 (± 2 months) and then yearly until year 5, or until disease progression.

Follow-up visits will be completed in-person unless the patient does not agree to continue in-person visits. In this case, telephone contact may be arranged to ensure the collection of as many safety and efficacy parameters as possible. The approach taken should be recorded in the CRF. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Patients who develop disease progression during combination therapy will be followed for a minimum of 30 days after the last dose of study drug or study procedure, or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event and disease progression, whichever occurs later.

6.7 General Concomitant Medication

Medications, including reason for use, date(s) of administration, and dosage information, taken within 28 days prior to the start of treatment will be recorded. Concomitant medications, including medications for AEs, will continue to be recorded up to 30 days after treatment discontinuation. This includes any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements. The investigator should be alerted if the patient is taking any agent known to affect the study agent(s) or with the potential for drug interactions. Following treatment discontinuation, information on subsequent anti-cancer therapies will be recorded.

Because there is a potential for interaction of Hu5F9-G4 (magrolimab) and Dinutuximab 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.

For all prohibited and/or restricted concomitant medications, treatment and supportive care while receiving protocol therapy, please refer to inclusion/exclusion criteria (section 3.0).
Pharmacologic doses of systemic corticosteroids should be used ONLY for life-threatening conditions (i.e. life-threatening allergic reactions and anaphylaxis such as bronchospasm, stridor) unresponsive to other measures. **The use of dexamethasone as an anti-emetic is not permitted.** Corticosteroid therapy can be used as a premedication for transfusion in patients known to have a history of transfusion reactions or for treatment of an unexpected transfusion reaction (hydrocortisone 2 mg/kg or less or an equivalent dose of an alternative corticosteroid). **The use of steroids during protocol therapy requires clear justification and documentation.**

Patients who use oral contraceptives should continue their use. Males and females of reproductive potential should use highly effective means of contraception (refer to section 6.8).

6.7.1 Hu5F9-G4 (magrolimab) Excluded Therapies

Any concomitant therapy intended for the treatment of cancer, whether health authority approved or experimental, is prohibited unless it is specifically included in the treatment regimen described in this protocol. There are no studies regarding drug-drug interactions conducted with Hu5F9-G4 (magrolimab).

6.7.2 Dinutuximab Excluded Therapies

Any concomitant therapy intended for the treatment of cancer, whether health authority approved or experimental, is prohibited unless it is specifically included in the treatment regimen described in this protocol. There are no studies regarding drug-drug interactions conducted with dinutuximab.

6.8 Contraception

The effects of Hu5F9-G4 (magrolimab) monoclonal antibody on the developing human fetus are unknown and dinutuximab is known to be teratogenic.

A woman is of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Females of childbearing potential must have a negative urine or serum pregnancy test within 30 days of enrollment and within 72 hours prior to treatment initiation. Additional pregnancy tests (serum or urine) should be obtained throughout the study in accordance with local policy.

Female patients of childbearing potential must be willing to use one highly effective method of contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, during the study and continue for 4 months after the last dose of study treatment. 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.

- Examples of contraceptive methods with a failure rate of < 1% per year include: bilateral tubal ligation, male sterilization, and established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
- Hormonal contraceptive methods must be supplemented by a barrier method plus spermicide.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

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.

7 DOSING DELAYS/DOSE MODIFICATIONS

The administration of Hu5F9-G4 (magrolimab) (in the "single agent Safety Lead-In" and/or during cycles of the combination cycles with Hu5F9-G4 (magrolimab) and dinutuximab) will be modified according to the attribution (possibly, probably or definitely related) to either Hu5F9-G4 (magrolimab) or dinutuximab.

The National Cancer Institute (NCI) CTCAE Version 5.0 will be used to grade AEs. Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in this section.

Patients will be evaluated for AEs (all grades), SAEs and AEs requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

The primary approach to mild AEs (Grades 1−2) is supportive and symptomatic care. The general approach to clinically significant and/or unacceptable toxicity (Grade 3 AEs) is holding study treatment until the toxicity resolves (≤ Grade 2) and then resume at one dose level lower, if clinically indicated. Supportive therapy must be administered per standard clinical practice. Consultation with the protocol PI and/or the PED-CITN Coordinating Center is required.

Adverse Event specific guidelines are provided below.

7.1 Dosage modification for Hu5F9-G4 (magrolimab)

Nausea	**Management/Next Dose for Hu5F9-G4 (magrolimab)**
≤ 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)**
≤ 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)**
≤ 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 with 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)**
≤ Grade 1	No change in dose
Grade 2	No change in dose.
Grade 3	No change in dose.
Grade 4	Hold until ≤ Grade 2. Resume at same dose level.*
*Patients requiring a delay of >2 weeks should go off protocol therapy.	

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

Anemia	**Management/Next Dose for Hu5F9-G4 (magrolimab)**
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3 hemolytic anemia that is	

Anemia	Management/Next Dose for Hu5F9-G4 (magrolimab)
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.
Grade 4	First occurrence: permanently discontinue unless patient is clinically benefitting.

7.2 Hu5F9-G4 (Magrolimab) AE Management and Dose Interruption Guidelines

For detailed information regarding management of AEs associated with Hu5F9-G4 (magrolimab), please refer to the most current version of the Hu5F9-G4 (magrolimab) Investigator's Brochure.

7.2.1 Management of Infusion-related Reactions (IRR)

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), 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 first two doses of Hu5F9-G4 (magrolimab) or in case of re-priming of Hu5F9-G4 (magrolimab), please refer to Table 5.

Recommendations for the management of IRRs are provided below.

Toxicity	Severity	Management
Infusion-related Reactions	Grade 1 – mild transient reaction	Remain at bedside and monitor patient until recovery from symptoms.
	Grade 2 - 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 (0.5 – 1 mg/kg, max 50 mg) IV (or equivalent) and/or 10 mg/kg, max dose 650 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

Toxicity	Severity	Management
		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.
	Grade 3 – 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) or Grade 4 - 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 0.01 mg/kg up to 0.5 mg of a 1:1,000 solution for subcutaneous administration or 0.01 mg/kg of a 1:10,000 solution injected slowly for IV administration and/or diphenhydramine 0.5 – 1 mg/kg IV with methylprednisolone 1 mg/kg 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 (10 mg/kg, max dose 650 mg), oral or IV diphenhydramine (0.5 – 1 mg/kg, max dose 50 mg), and IV dexamethasone (0.6 mg/kg), 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 generalized pruritus after Day 1 but within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

7.2.2 Magrolimab Dosing Guidance for Planned Surgical Procedures

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

Abbreviations: CNS = central nervous system

7.2.3 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), and serum chemistries testing as outlined in the schedule of assessments (SOA).

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

Hemoglobin level must be documented as detailed in section 6.2.1.3. Patients with a low baseline hemoglobin 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 must 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.

Before Exposure to Hu5F9-G4 (magrolimab)

In participants who have not been transfused in the preceding 3 months, an extended RBC phenotyping including minor antigens (Rh CcDEe, Cw, MNSs, K [k if K+] Fya, Fyb, Jka, and Jkb) should be performed at screening. In these participants, blood genotyping (that includes minor antigens Rh CcDEe, Cw, MNSs, K [k if K+] Fya, Fyb, Jka, and Jkb) is acceptable as an alternative to extended phenotyping.

Because transfused blood can interfere with RBC phenotyping assessment, participants who received blood transfusion in the preceding 3 months should have their blood genotype documented at screening, and for these participants extended RBC phenotyping is not sufficient and does not need to be performed.

Results should be available before the first dose of magrolimab.

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

In case ABO/Rh type cannot be resolved, use pretreatment phenotype/genotype matched units for ABO, Rh and other minor RBC antigens (CcDEe and Kk, to the feasible extent).

7.2.5 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.

7.2.6 Management of Pneumonitis

Pneumonitis has been infrequently observed in patients receiving 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, etc.). If a non-inflammatory cause is 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 is detailed below and follows American Society of Clinical Oncology (ASCO) guidelines for immune-related adverse events (Brahmer et al., 2018). Patients who experience Grade 3-4 pneumonitis will be permanently discontinued from study treatment.

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

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

7.2.7 Management of 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.

7.3 **Dinutuximab (Unituxin®)** AE Management and Dose Modification Guidelines

For detailed information regarding management of AEs associated with dinutuximab (Unituxin®), please refer to the most

current version of the dinutuximab (Unituxin®) prescribing information.

The most common adverse drug reactions (≥ 25%) with dinutuximab are pain, pyrexia, thrombocytopenia, lymphopenia, infusion reactions, hypotension, hyponatremia, increased alanine aminotransferase, anemia, vomiting, diarrhea, hypokalemia, capillary leak syndrome, neutropenia, urticaria, hypoalbuminemia, increased aspartate aminotransferase, and hypocalcemia.

7.3.1 Discontinuation of Dinutuximab

The administration of dinutuximab will be discontinued for the following adverse events that are possibly, probably or definitely related to dinutuximab administration:

Table 8: Adverse Reactions Requiring Permanent Discontinuation of Dinutuximab

Severity	Adverse Reaction
Grade 3 or 4	Anaphylaxis
Grade 3 or 4	Serum sickness
≥Grade 3	Pain unresponsive to maximum supportive measures
Grade 4	Sensory neuropathy
Grade 3	Sensory neuropathy that interferes with daily activities for more than 2 weeks
≥Grade 3	Peripheral motor neuropathy
≥Grade 3	Decrease in vision if not improved to Grade 1 or better before next dose is due.
Grade 4	Hyponatremia despite appropriate fluid management

7.3.2 Dose Modification of Dinutuximab

The administration of dinutuximab will be modified for the following adverse events that are possibly, probably or definitely related to dinutuximab administration.

7.3.2.1 Treatment of dinutuximab-induced hypotension (without evidence of allergic reaction)

a. If hypotension is severe and accompanied by poor perfusion, end organ dysfunction, or acidemia – Pediatric Advanced Life Support (PALS) guidelines should be followed and dinutuximab infusion discontinued.

b. In the absence of poor perfusion, end organ dysfunction or acidemia, moderate hypotension is defined as:

   i. Symptomatic decreases in blood pressure (BP) and/or
   ii. Systolic BP < 5th percentile based on age and height and baseline BPs OR
   iii. Systolic or diastolic BP decrease by > 20% below baseline.

c. For patients with moderate hypotension in the absence of poor perfusion, end organ dysfunction, or acidemia:

   i. Immediately hold dinutuximab
   ii. Give normal saline bolus (20 mL/kg as rapidly as possible)
   iii. Stop or adjust doses of narcotics and sedating H1 blockers
   iv. Consider use of Trendelenberg position

d. If hypotension persists after the above measures have been taken:

i. Reassess perfusion and end organ function
ii. Follow PALS algorithm if indicated
iii. Repeat NS bolus OR
iv. Consider use of albumin if albumin < 3 gm/dL
v. Consider use of RBCs if Hb < 10 gm/dL
vi. Consider use of platelets if count < 50,000/uL
vii. Consider transfer to intensive care unit.

e. If hypotension persists after 2 volume boluses, give an additional bolus and prepare to administer pressors

i. Epinephrine or norepinephrine is preferred over dopamine if possible

f. Resumption of dinutuximab

i. For patients whose hypotension resolves promptly and completely with limited volume resuscitation (≤ 40 mL/kg) and without requirement for pressor support, dinutuximab may be restarted at 50% of the previous infusion rate. The dinutuximab may be restarted on same day if it is possible to do so within 20 hours of the start of the day's infusion. If blood pressures are stable for 2 hours, the infusion may be given at full rate for that day and subsequent days. If the patient again experiences hypotension requiring multiple volume boluses (e.g., > 40 mL/kg) when dinutuximab is given at full rate but tolerates the 50% infusion rate, the remaining days' doses of dinutuximab should be given at the 50% rate of infusion. If > 20 hours have elapsed since the start of the infusion, restart dinutuximab the following day.

1. If blood pressures are stable for 2 hours after resumption of dinutuximab at the reduced rate, the remainder of the antibody infusion may be given at the full rate
2. If hypotension recurs at the reduced rate, the measures above should again be taken and no further dinutuximab should be given that day. The antibody infusion may be restarted the following day after ensuring that the patient is volume replete. The antibody rate upon resumption of treatment should be 50% of the initial rate. If blood pressures are stable for 2 hours, the infusion may be given at full rate for that day and subsequent days. If the patient's blood pressures are only stable at the 50% rate and not at full rate, the remaining days' doses of dinutuximab should be given at the 50% rate of infusion.

ii. For patients who require multiple volume boluses for hemodynamic stabilization, dinutuximab should be resumed the following day at 50% of the initial infusion rate.

1. If blood pressures are stable for 2 hours after resumption of dinutuximab at the reduced rate, the remainder of the antibody infusion may be given.
2. If hypotension recurs at the reduced rate, the measures above should again be taken and no further dinutuximab should be given that day. The antibody infusion may be restarted the following day after ensuring that the patient is volume replete. The antibody rate upon resumption of treatment should be 50% of the initial rate. If blood pressures are stable for 2 hours, the infusion may be given at full rate for that day and subsequent days. If the patient's blood pressures are only stable at the 50% rate and not at full rate, the remaining days' doses of dinutuximab should be given at the 50% rate of infusion.

iii. For patients who require pressors for treatment of hypotension, if blood pressure is stable off pressors for at least 6 hours, administration of dinutuximab may be resumed at 50% of the initial infusion rate on the day following the hypotensive episode. Care should be taken to ensure that the patient is volume replete. Dinutuximab should not be given to patients who continue to require pressor support. Patients who require pressor support for ≥ 24 hours due to treatment-related hypotension despite appropriate volume resuscitation should discontinue protocol therapy. Patients

who again require pressor support when dinutuximab is resumed should discontinue protocol therapy.

7.3.2.2 Treatment of Allergic Reactions/Infusion Reactions

a. Mild allergic reactions/infusion reactions to dinutuximab infusion

i. A mild allergic reaction is limited to rash, flushing, urticaria, mild dyspnea – Grade 1 or 2

ii. The following recommendations do NOT apply to Grade 3 or 4 allergic reactions, including anaphylaxis

iii. Management

- Decrease rate of dinutuximab to 50% of full rate
- Perform serial exams at bedside
- Administer H1 blocker (diphenhydramine, cetirizine recommended)
- Administer H2 blocker
- When symptoms resolve, resume original infusion rate
- If symptoms recur when original rate is resumed, decrease to 50% rate again
- Infusion must be stopped after 20 hours (whether the full dose of dinutuximab has been administered or not); document total amount of drug given in the 20-hour time period

b. Moderate to severe allergic reactions/infusion reactions to dinutuximab infusion

i. Moderate to severe reactions include any of the following: symptomatic bronchospasm, allergy-related edema/angioedema, hypotension, or anaphylaxis – Grade 3 or 4

ii. The following recommendations do NOT apply to Grade 1 or 2 allergic reactions

iii. Management: **Immediately hold** dinutuximab

- Assess airway, breathing and circulation
- Follow institutional guidelines for rapid response team notification if clinically indicated
- For airway concerns
  - Administer oxygen and albuterol immediately for bronchospasm
  - Administer IV diphenhydramine
  - Administer epinephrine (1:1000 IM recommended) immediately if upper airway involved or if airway issues are accompanied by cardiovascular collapse
  - Administer IV hydrocortisone (1-2 mg/kg) if the patient has frank anaphylaxis with cardiorespiratory collapse OR if ≥ 2 doses of epinephrine are required OR if moderate to severe symptoms recur upon rechallenge with dinutuximab
- For hypotension in the setting of allergic reaction
  - Give normal saline bolus (20 mL/kg as rapidly as possible)
  - Stop or adjust doses of narcotics and sedating H1 blockers
  - Consider use of Trendelenberg position
  - See previous section for management of persistent hypotension
- For patients with mild bronchospasm or angioedema that does not impact breathing, completely resolves without the use of epinephrine and hydrocortisone and for patients whose hypotension resolves following volume bolus, dinutuximab may be resumed at 50% of the previous rate of infusion on the same day as the reaction occurred. If symptomatic angioedema or asymptomatic bronchospasm recurs when the dinutuximab is restarted, discontinue immunotherapy for that day and if symptoms/signs resolve completely that day, resume the next day with additional

pre-medication of hydrocortisone 1-2 mg/kg IV. For this re-challenge, the infusion should be given in an ICU setting.

- For patients whose bronchospasm or angioedema requires the use of systemic epinephrine, protocol therapy should be discontinued.
- For patients with bronchospasm or angioedema that does not require systemic epinephrine but whose hypotension requires more extensive volume resuscitation, guidance in **Section 7.3.2.1** should be followed.

7.3.2.3 Management of capillary leak syndrome (≥ Grade 3)

a. Hold dinutuximab infusion
b. Provide oxygen, fluids as needed
c. Diuretics should be used with caution and hypotension avoided
d. See **Section 7.3.2.1** for management of hypotension, anemia and hypoalbuminemia
e. Do NOT resume dinutuximab therapy if symptoms of severe capillary leak syndrome persist on the same day or subsequent days of a given cycle. Only resume dinutuximab therapy when the capillary leak syndrome resolves or requires less significant intervention (Grade 2 or less).
f. If capillary leak resolves, may resume dinutuximab infusion at 50% rate the same day and for subsequent doses during a given cycle. The infusion may be given at the full rate at the start of subsequent cycles
g. If mechanical ventilation (any duration) or pressor support for ≥ 24 hours is required due to therapy-related capillary leak syndrome, the patient should discontinue protocol therapy.

7.3.2.4 Management of renal insufficiency (unrelated to hypotension)

a. Consider the possibility of renal hypoperfusion in the context of borderline hypotension; administer volume if appropriate
b. If the patient's creatinine is elevated to ≥ 2 x the upper limit of normal for age/gender (see table in Section 3.2.6.2) and elevation persists despite optimized fluid management, hold dinutuximab
c. Modify dosing of concomitant medications that may contribute to or be affected by renal insufficiency
d. When urine output returns to normal and creatinine returns to < 2 x upper limit of normal for age/gender, resume dinutuximab at 50% rate. If renal function normalizes by the following day, dinutuximab may be administered at full rate. If renal function is not sufficiently improved (urine output normal and creatinine < 2x ULN for age/gender) by Day 7, no further dinutuximab should be given during that cycle of therapy. If renal function has normalized by the planned start date for the next cycle, retreatment with dinutuximab is permitted

7.3.2.5 Management of hyponatremia (≥ Grade 3; Na < 130 mEq/L and symptomatic or 120-124 mEq/L regardless of symptoms)

a. Change hypotonic fluids to isotonic fluids as compatibilities permit
b. Avoid administration of oral free water
c. Correct fluid losses due to diarrhea
d. 3% saline is only indicated in the following settings:
    - hyponatremia leading to seizure
    - drop in sodium level > 10 points in 6 hours or less
    - sodium level < 117 mEq/L
e. If Grade 4 hyponatremia persists despite optimal fluid management, discontinue dinutuximab for the remainder of the cycle. Sodium should be monitored closely during the next cycle of therapy. If hyponatremia improves to Grade 2 or better, or baseline, empiric dose reduction is not required at the start of the next cycle of therapy, though dinutuximab would again be discontinued if Grade 4 hyponatremia were to persist despite optimal fluid management. In such cases, patient should discontinue protocol therapy.

7.3.2.6 Management of fever in the absence of hypotension

a. Administer antipyretics
b. Adjust fluids to account for insensible losses if fever is persistent
c. Obtain blood culture
d. Administer empiric antibiotics if suggested by institutional policy

7.3.2.7 Management of treatment-related pain

a. No further dinutuximab therapy should be given to patients who experience treatment related Grade 3 pain that cannot be controlled by narcotics during a given cycle. Treatment with gabapentin or similar agent should be initiated if not already being administered. If pain that is not controlled with narcotics recurs during a subsequent cycle, the patient should discontinue protocol therapy
b. For patients with treatment-related Grade 3 pain requiring intravenous narcotics for ≥ 48 hours following completion of dinutuximab therapy, gabapentin or similar agent should be initiated if not already being administered. If pain requiring prolonged intravenous narcotics (≥48 hours following completion of dinutuximab therapy) recurs during a subsequent cycle despite this intervention, the patient should discontinue protocol therapy.

7.3.2.8 Management of visual changes

a. Dinutuximab may cause impaired accommodation and/or dilated pupils with sluggish light reflex with or without photophobia. No dose modifications, dose reductions, or changes in infusion rate should be made unless there is associated vision loss. If this occurs in conjunction with Grade 3 decrease in vision, dinutuximab should be discontinued. If visual loss improves to Grade 1 or better before the next immunotherapy course is due, the patient should receive dinutuximab at a dose that is 50% reduced compared to the prior dose. If the lower dose of dinutuximab is tolerated without worsening of ocular toxicity, full dose dinutuximab should be given in subsequent courses. If visual toxicity worsens, the patient should discontinue protocol therapy.
b. Dose reductions for dilated pupils or changes in accommodation without vision loss are not required.

7.3.2.9 Management of serum sickness

a. Identification of serum sickness – signs and symptoms include arthralgias/arthritis, splenomegaly, lymphadenopathy, glomerulonephritis in the presence of persistent fevers, cutaneous eruptions.
b. Serum sickness typically develops 1 to 3 weeks after administration of the causative agent but can develop within 12-36 hours in patients who have previously been sensitized to the causative agent.
c. Patients with ≥ Grade 3 serum sickness should discontinue protocol therapy.
d. For Grade 2 serum sickness, antihistamines should be prescribed.

7.3.2.10 Management of neurotoxicity

a. Patients who develop Grade 4 neurotoxicity should discontinue protocol therapy.
b. Dinutuximab should be discontinued for the remainder of the current cycle of therapy for patients who develop Grade 3 sensory neuropathy or Grade 3 motor neuropathy. If abnormalities resolve by start of next cycle of therapy, the patient may receive 50% dose of dinutuximab (i.e., dinutuximab dose 8.75 mg/m^2). If symptoms do not completely resolve or recur with dinutuximab then the patient should discontinue protocol therapy.

8 AGENT 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(s)

8.1.1 Hu5F9-G4 (magrolimab), NSC 809249

Other names: Magrolimab or 5F9

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 (magrolimab) 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: Hu5F9-G4 (magrolimab) injection is an investigational agent supplied by Gilead and distributed to investigators by the CTEP Division of Cancer Treatment and Diagnosis (DCTD), NCI as 200 mg/10 mL (20 mg/mL) single-use vials in a type I borosilicate glass vial with butyl rubber stopper and aluminum seal. 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, pH 5.0, and sterile water for injection. Hu5F9-G4 (magrolimab) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see **Section** Error! Reference source not found.).

Preparation: Acceptable IV bags are: Polyvinyl chloride (PVC) preferably without DEHP or non-PVC alternatives such as ethylene vinyl acetate, polypropylene (ViaFlo®) or combination of ethylene and polypropylene (Excel® or IntraVia®).

The following proprietary closed system transfer devices (CSTDs) are compatible with magrolimab: PhaSeal, PhaSea Optima, Equashield, Chemolock^{T}, SmartSite with Texium and Spiros.

- 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. A 250 mL 0.9% sodium chloride may be used to prepare doses for subjects with volume restriction. Refer to the table below for the total infusion volumes for each age group.

- Obtain the required number of vials from stock and examine them for discoloration, cloudiness or particles. Do not use if particulate matter or discoloration is noted.
- Remove the equivalent Hu5F9-G4 (magrolimab) calculated dose volume from the 250 mL or 500 mL IV bag if using a prefilled 0.9% sodium chloride IV bag.

- Add the calculated dose volume of Hu5F9-G4 (magrolimab) into the 0.9% sodium chloride IV bag.
- 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.

Total Infusion Volume per Age Group

Age Group	Priming Infusion Volume (mL) – infused over 3 hours (+/- 30 minutes)	Maintenance Infusion Volume (mL) – infused over 2 hours (+/- 10 minutes)
≥1 year to < 2 years	50	100
2 years to < 6 years	250	250
6 years to < 12 years	250	250
12 years to < 18 years	250	500
Adult	250	500

The prepared IV solution can be stored at 25^0 C and must be used within 8 hours of preparation. Discard the prepared IV solution if exceeding 8 hours. Do not refrigerate the prepared IV solution. There is no stability data to support the prepared IV solution stored at 2°C - 8°C (36° F to 46° F).

Do not mix with any other drug in the infusion bag or administration set.
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 in Cycle 1 Day 1. The priming dose (1 mg/kg) will be infused over 3 hours (+/- 30 minutes) via a peripheral or central line. Protecting IV bag from light is not required. In-line IV filter set is not required. Subsequent IV doses are to be infused over 2 hours (+/- 10 minutes)**.**

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. 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 Section 6.8 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.

If the study agent is provided by the NCI under a Collaborative Agreement with the agent manufacturer, the text below must be included in the protocol. Information on the study agent's Collaborative Agreement status will be provided in the approved LOI response letter.

Hu5F9-G4 (magrolimab) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see **Section** Error! Reference source not found.).

8.1.2 Dinutuximab (Chimeric Monoclonal Antibody 14.18 (UTC)), NSC 764038

Other Names: Chimeric Monoclonal Antibody 14.18 (UTC); human/murine anti-G_{D2} monoclonal antibody; chimeric anti-G_{D2}; chimeric mAb 14.18; ch14.18
Classification: Chimeric/human monoclonal antibody

Description: Dinutuximab, Chimeric MOAB 14.18 (UTC) is an anti-G_{D2} monoclonal antibody composed of the variable region heavy and light chain genes of the murine mAb 14.G_{2a} and the human constant region genes for heavy chain IgG_1 and light chain kappa.

Mode of Action: Dinutuximab exerts its antitumor effect by binding specifically to the disialoganglioside G_{D2}, an antigen found in human tumors of neuroectodermal origin such as melanoma and neuroblastoma. This chimeric antibody has been shown to lyse melanoma and neuroblastoma cells through the process of antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity. By targeting the G_{D2} antigen on the cell surface, chimeric MOAB 14.18 may also prevent attachment of circulating malignant cells to the extracellular matrix.
Additionally, dinutuximab mediates lysis of several melanoma and neuroblastoma cells lines in a dose dependent manner in the presence of potent mediators of chimeric MOAB 14.18-dependent cytotoxicity, such as human peripheral blood mononuclear cells and granulocytes, in particular neutrophils, especially in the presence of recombinant human granulocyte-macrophage colony-stimulating factor.

How Supplied: Dinutuximab is manufactured by United Therapeutics and distributed by the CTEP, DCTD, NCI.
Do not use commercial supply. Dinutuximab is provided as a sterile solution in single-dose vials containing 17.5 mg/5 mL (3.5 mg/mL) in 20 mM Histidine, 150 mM NaCl, 0.05% Tween 20 at pH 6.8.
Dose: 17.5 mg/m^2/dose

Preparation: Withdraw the required dose of chimeric dinutuximab from the vial(s) and inject the exact volume for the 17.5 mg/m^2/day dose into a 100 mL bag of 0.9% sodium chloride. The use of a filter during preparation is not required.

Route of Administration: Intravenous (IV) infusion.

Method of Administration: The dose will be administered by IV infusion over 10-20 hours per **Figure 2**.

Storage and Handling: Intact vials should be stored in the refrigerator (2ºC to 8ºC).

Stability: Stability studies of the intact vials are ongoing. Dinutuximab is stable at room temperature for at least 24 hours when diluted to a concentration between 0.044 mg/mL and 0.56 mg/mL; however, the final dosage form should be prepared immediately prior to administration as there is a maximum infusion time of 20 hours. The minimum infusion time for the antibody infusion is 10 hours.

If a storage temperature excursion is identified, promptly return ch14.18 (dinutuximab) to the refrigerator temperature 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.

8.1.3 Agent Ordering and Agent Accountability

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 patient enrollment is required for starter supply.

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 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.

8.1.3.1 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.

8.1.4 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.

8.1.5 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP 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 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)

9 STATISTICAL CONSIDERATIONS

9.1 Responsibility for Analyses

The statistical analysis of the data obtained from this trial will be the responsibility of Fred Hutchinson Cancer Center as part of the Pediatric CITN.

9.2 Study Design/Endpoints

9.2.1 Dose Finding Cohort (Arm A) Primary Endpoint

The primary objective is to determine the safety and tolerability of Hu5F9-G4 (magrolimab) in combination with dinutuximab in children and young adults with relapsed/refractory (R/R) neuroblastoma (NBL) and osteosarcoma, and to determine the recommended phase 2 dose (RP2D) of Hu5F9-G4 (magrolimab) given in combination with dinutuximab. All patients who receive any amount of the study drug will be evaluable for toxicity. There will be two timepoints at which dose limiting toxicities (DLTs) will be measured to establish the maximum tolerated dose (MTD): during the 'single agent Safety Lead-In' in which patients with osteosarcoma or NBL will receive Hu5F9-G4 (magrolimab) during the first 3 weeks, and during Cycle 1 (21 days) of the combination of Hu5F9-G4 (magrolimab) and dinutuximab (**Figure 2**) as described in **Section 6.3**. If patients in the 'single agent Safety Lead-in' cohort or during Cycle 1 combination of Hu5F9-G4 (magrolimab) and dinutuximab discontinue participation prior to the safety evaluation for reasons other than the occurrence of a DLT (*e.g.,* withdrawal of consent, rapid tumor progression, death due to rapid tumor progression, AE that does not meet DLT criteria), they will not be evaluable for MTD and will be replaced in the appropriate dose-finding group ('single agent Safety Lead-In' or Cycle 1 of Arm A).

If a patient is replaced to determine safety in Cycle 1 of Arm A, and the dose of Hu5F9-G4 (magrolimab) has NOT been deemed safe, i.e., 3 patients have not completed the Safety Lead-in without DLT, the replaced patient will undergo priming dose of Hu5F9-G4 (magrolimab), undergo the Safety Lead-in and then proceed to Cycle 1. This patient will be evaluable for DLT in the Safety Lead-in group.

If 3 patients have received Hu5F9-G4 (magrolimab) during the Safety Lead-in and the dose of Hu5F9-G4 (magrolimab) has been deemed safe, a patient being replaced in Cycle 1 of Arm A, will undergo a priming dose of Hu5F9-G4 (magrolimab) and proceed directly to Cycle 1 (combination of Hu5F9-G4 (magrolimab) and dinutuximab) for determination of MTD in the combination cohort.

Establishment of safety of the combination of Hu5F9-G4 (magrolimab) and dinutuximab will be completed in the first 3 patients enrolled in Arm B as described in section 6.1.1.2.
The safety and tolerability of Hu5F9-G4 (magrolimab) plus dinutuximab will be assessed by:

- Suspected adverse events, and
- Suspected serious adverse events

As evidenced by:

- Changes in clinical laboratory tests (clinical chemistry, hematology, etc).

- Changes in vital signs (blood pressure, pulse, respiratory rate and body temperature).
- Changes in physical exams. Signs and symptoms assessed may require additional testing as clinically indicated such as ECG, PFT, radiographic studies, etc.
- Subject reported signs and symptoms

Safety data will be analyzed per standard methods and interpreted descriptively. Safety data will be summarized for each disease group separately and for both disease groups combined. Adverse events will be assessed using the CTCAE version 5.0 for type and severity of event. Serious Adverse Events will be summarized for each disease group and for both disease groups combined. Reasons for discontinuation of study therapy will be tabulated.

9.2.2 Expansion Cohorts B1-3 (Arm B) Primary Endpoint

The primary objective for the expansion cohorts is to Evaluate the Overall Response Rate (ORR) of patients treated with Hu5F9-G4 (magrolimab) at RP2D and dinutuximab (see **Figure 2**) as per **Section** Error! Reference source not found.. The three expansion cohorts are defined as:

Cohort B1: Patients with relapsed/refractory confirmed NBL: measurable NBL/ganglioneuroblastoma;

Cohort B2: Patients with relapsed/refractory evaluable NBL; and

Cohort B3: Patient with relapsed/refractory measurable osteosarcoma.

Each cohort will be evaluated for response which will include a stopping rule for futility as follows:

Expansion Cohort B1

	Cumulative Number of Responses	**Decision**
Stage 1: Enter 10 patients	0	Terminate this cohort: agent ineffective
	1 or more	Inconclusive result, continue cohort to enroll to stage 2
Stage 2: Enter additional 10 patients	2 or less	Terminate this cohort: agent ineffective
	3 or more	Terminate this cohort: agent effective

Measurable soft tissue disease will be evaluated as per the International Neuroblastoma Response Criteria (INRC) (Park et al., 2017), and responses will be determined as either complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). Response rates will be calculated for the confirmed neuroblastoma cohort whose best response is a CR or PR. Response is defined relative to baseline disease. This combination will not be considered to be of sufficient interest for further evaluation if the true response rate is 5% and of sufficient activity if the true response rate is 25%. If the combination has a true response rate of 5%, the rule described above will identify it of sufficient activity for further study with a probability of 0.07 (type1 error) and the trial will have an expected sample size of 14 with 60% probability of early termination. If the combination has a true response rate of 25%, the rule described above will identify it of sufficient activity for further study with probability 0.88 (power against the alternative hypothesis P = 0.25).

Expansion Cohort B2

Evaluable disease will be evaluated with ^{123}I-MIBG in conjunction with anatomical imaging or bone marrow aspiration;

FDG-PET may be used for tumors that are not MIBG-avid as per the International Neuroblastoma Response Criteria (INRC). Overall response rate (ORR) as measured by INRC: Initially 10 eligible subjects will be treated with Hu5F9-G4 (magrolimab) and dinutuximab at RP2D (including those in the safety evaluation); if 0 responses occur, enrollment will stop to this cohort. If 1 or more subjects respond, enrollment will continue to a total of 20 subjects with evaluable neuroblastoma treated at the RP2D. If 3 or more evaluable subjects with evaluable disease have a response, this combination in this cohort will be considered of sufficient interest to warrant additional study. The following Simon's optimal two stage design will be used for this cohort:

	Cumulative Number of Responses	**Decision**
Stage 1: Enter 10 patients	0	Terminate this cohort: agent ineffective
	1 or more	Inconclusive result, continue cohort to enroll to stage 2
Stage 2: Enter additional 10 patients	2 or less	Terminate this cohort: agent ineffective
	3 or more	Terminate this cohort: agent effective

The response criteria for this cohort will be as defined in INRC. Responses will be determined as either complete response (CR), partial response (PR), stable disease (SD), minor response (MR), or progressive disease (PD). Response rates will be calculated for the confirmed neuroblastoma cohort whose best response is a CR or PR. Response is defined relative to baseline disease. This combination will not be considered to be of sufficient interest for further evaluation if the true response rate is 5% and of sufficient activity if the true response rate is 25%. If the combination has a true response rate of 5%, the rule described above will identify it of sufficient activity for further study with a probability of 0.07 (type1 error) and the trial will have an expected sample size of 14 with 60% probability of early termination. If the combination has a true response rate of 25%, the rule described above will identify it of sufficient activity for further study with probability 0.88 (power against the alternative hypothesis P = 0.25).

Expansion Cohort B3

Overall response rate (ORR) as measured by RECIST v1.1: Initially 10 eligible subjects will be treated with Hu5F9-G4 (magrolimab) and dinutuximab at RP2D; if 0 responses (PR or CR) occur, enrollment will stop to this cohort. If 1 or more subjects respond, enrollment will continue to a total of 20 subjects with measurable osteosarcoma treated at the RP2D. If 3 or more evaluable subjects with measurable disease have a response, this combination in this cohort will be considered of sufficient interest to warrant additional study. The following Simon's optimal two stage design will be used for this cohort:

	Cumulative Number of Responses	**Decision**
Stage 1: Enter 10 patients	0	Terminate this cohort: agent ineffective
	1 or more	Inconclusive result, continue cohort to enroll to stage 2
Stage 2: Enter additional 10 patients	2 or less	Terminate this cohort: agent ineffective
	3 or more	Terminate this cohort: agent effective

Measurable soft tissue disease will be evaluated using either CT or MRI, and lesions will be measured according to RECIST

v1.1., and responses will be determined as either complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). Response rates will be calculated for the osteosarcoma cohort whose best response is a CR or PR. Response is defined relative to baseline disease. This combination will not be considered to be of sufficient interest for further evaluation if the true response rate is 5% and of sufficient activity if the true response rate is 25%. If the combination has a true response rate of 5%, the rule described above will identify it of sufficient activity for further study with a probability of 0.07 (type1 error) and the trial will have an expected sample size of 14 with 60% probability of early termination. If the combination has a true response rate of 25%, the rule described above will identify it of sufficient activity for further study with probability 0.88 (power against the alternative hypothesis P = 0.25).

9.2.3 Expansion Cohort B4 Primary Endpoint

The primary objective for the expansion cohort B4 is to determine the safety and feasibility of administering Hu5F9-G4 (magrolimab) in combination with dinutuximab to patients that undergo recent resection of metastatic osteosarcoma within three weeks of surgery.

Ten (10) evaluable subjects will be treated with Hu5F9-G4 (magrolimab) and dinutuximab at RP2D. If 3 or more subjects out of the 10 subjects experience complications, the lower bound of the 95% Clopper-Pearson confidence interval on the proportion of complications will be higher than 5%. Thus, if 3 or more subjects out of the 10 subjects experienced complications, the use of Hu5F9-G4 (magrolimab) in combination with dinutuximab after surgery would be considered not feasible.

9.3 Sample Size/Accrual Rate

9.3.1 Proposed Sample Size

A minimum of 4 patients and a maximum of 82 patients will be enrolled on this trial.

9.3.2 Accrual Rate

The expected accrual is 2-3 patients per month (slower during dose escalation, more rapid during expansion cohorts). We estimate that accrual will be completed within about 36 months.

9.3.3 Sample Size Justification

A minimum of 4 patients will be enrolled on this trial if two patients at Dose Level 1 have DLTs and 2 patients at Dose Level -1 have DLTs.

A maximum of 82 patients will be enrolled on this trial:

- Six patients/dose level at Dose Level 1 and Dose Level -1 = 12
- Three expansion cohorts (B1, B2 and B3) of 20 patients in each cohort
- Ten patients in cohort B4.

9.4 Demographics

This trial is open to all participants regardless of gender or ethnicity. Efforts will be made to extend the accrual to a representative population; however, in a Phase1 trial, which will accrue a limited number of patients, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the

other. If differences in outcome that correlate to gender, racial or ethnic identity are noted, accrual may be expanded, and/or additional studies may be performed to investigate those differences more fully.

PLANNED ENROLLMENT REPORT

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	4	0	0	**7**
Native Hawaiian or Other Pacific Islander	1	2	0	0	**3**
Black or African American	5	6	0	0	**11**
White	15	22	7	9	**53**
More Than One Race	2	3	1	2	**8**
Total	**26**	**37**	**8**	**11**	**82**

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9.5 Analysis of Secondary Endpoints

9.5.1 Determine the pharmacokinetics (PK) of Hu5F9-G4 (magrolimab) in children and young adults.

The endpoint for PK analysis is to assess the drug concentrations achieved during this first in child trial. Samples will be collected in the Safety Lead-In cohort and the first 3 patients on any expansion cohorts on the following schedule:

- Safety Lead-In: Day 1, Day 8, Day 15
- Cycle 1: Day 1, Day 8, Day 15
- Cycle 2, 3, 5, 7, 9, 11: Day 1
- End of Therapy

These samples will be a mandatory in the Safety Lead-In cohort and in the first three patients on any expansion cohorts (B1, B2, B3 and B4).

The PK Analysis Set will be used for summaries of PK concentration of magrolimab versus time. Serum concentrations will be listed and summarized for magrolimab using descriptive statistics by sampling timepoint and cohort. Graphical plots of individual serum concentration versus time and mean concentration versus time by cohort will be generated.
The samples will be tested and analyzed by PPD.

9.5.2 Observe and record anti-tumor activity

Although the clinical benefit of this combination of 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.

All eligible patients will be considered evaluable for response if they receive any doses of the combination regimen. Antitumor activity will be evaluated in patients with osteosarcoma according to **Section 12.1** and in patients with neuroblastoma according to **Section 12.2**.

9.5.3 Evaluate the Event Free Survival (EFS) in two cohorts of osteosarcoma patients who are treated at the RP2D (measurable relapsed osteosarcoma and patients with pulmonary relapse undergoing resection) and compare to historical controls (Lagmay et al., 2016).

In this trial EFS is defined as the time from the first dose of Hu5F9-G4 (magrolimab) until the earliest of: death, local recurrence, new metastatic disease, progression of metastatic disease or secondary malignancy, or date of last contact. The historical control report of EFS for 96 patients with osteosarcoma and measurable disease was 12% at 4 months (95% CI, 6% to 19%). This study will compare the EFS of patients in the expansion cohort 3 (measurable osteosarcoma) to these historical controls.

10 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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)

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.

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.

10.1.1 CAEPRs for CTEP IND Agent(s)

10.1.1.1 CAEPRs for Hu5F9-G4 (magrolimab), NSC 809249

Below is the CAEPR for Hu5F9-G4 (magrolimab). Frequency is based on 1328 patients.

Version 2.2, December 6, 2023[1]

Adverse Events with Possible Relationship to Hu5F9-G4 (Magrolimab) (CTCAE 5.0 Term) [n= 1328]			**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)***
		Blood and lymphatic system disorders - Other (red blood cell agglutination)	
	Febrile neutropenia		***Febrile neutropenia (Gr 2)***
		Hemolysis	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	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)***
	Generalized edema		
INFECTIONS AND INFESTATIONS			
	Lung infection		
		Sepsis	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Infusion related reaction			***Infusion related reaction (Gr 2)***
INVESTIGATIONS			
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hypokalemia		***Hypokalemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			

Adverse Events with Possible Relationship to Hu5F9-G4 (Magrolimab) (CTCAE 5.0 Term) [n= 1328]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Cough		
	Dyspnea		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		
VASCULAR DISORDERS			
Hypotension			

[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 - Thrombotic thrombocytopenic purpura
GASTROINTESTINAL DISORDERS - Colitis; Constipation; Mucositis oral; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Pain
IMMUNE SYSTEM DISORDERS - Serum sickness
INFECTIONS AND INFESTATIONS - Conjunctivitis; Urinary tract infection
INVESTIGATIONS - Alkaline phosphatase increased; Aspartate aminotransferase increased
METABOLISM AND NUTRITION DISORDERS - Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Edema cerebral; Intracranial hemorrhage; Nervous system disorders - Other (cerebral hemorrhage)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Epistaxis; Hypoxia; Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Rash acneiform; Rash maculo-papular
VASCULAR DISORDERS - Hypertension; Thromboembolic event

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.

10.1.1.2 CAEPR for Dinutuximab (MoAb 14.18 chimeric (CH14.18)), NSC 764038

Below is the CAEPR for Dinutuximab (MoAb 14.18 chimeric (CH14.18)). Frequency is based on 359 patients.

Version 2.9, January 10, 2019[1]

Adverse Events with Possible Relationship to MoAb 14.18, chimeric (CH14.18) (CTCAE 5.0 Term) [n= 359]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Disseminated intravascular coagulation		***Disseminated intravascular coagulation (Gr 2)***
		Hemolytic uremic syndrome[2]	
CARDIAC DISORDERS			
		Cardiac arrest	
		Sinus bradycardia	
	Sinus tachycardia		***Sinus tachycardia (Gr 3)***
EYE DISORDERS			
		Eye disorders - Other (eye disorders)[3]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Diarrhea		***Diarrhea (Gr 3)***
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fever			***Fever (Gr 3)***
	Generalized edema		
Pain			***Pain (Gr 3)***
		Sudden death NOS	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 3)***
		Anaphylaxis	
	Serum sickness		
INFECTIONS AND INFESTATIONS			
	Infection[4]		***Infection[4] (Gr 3)***
		Myelitis[5]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Creatinine increased		***Creatinine increased (Gr 2)***
Investigations - Other (elevated c-reactive proteins)			***Investigations - Other (elevated c-reactive proteins) (Gr 2)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***

Adverse Events with Possible Relationship to MoAb 14.18, chimeric (CH14.18) (CTCAE 5.0 Term) [n= 359]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Neutrophil count decreased		***Neutrophil count decreased (Gr 3)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Hyperkalemia		***Hyperkalemia (Gr 2)***
	Hypoalbuminemia		***Hypoalbuminemia (Gr 3)***
	Hypocalcemia		
	Hypokalemia		***Hypokalemia (Gr 4)***
	Hyponatremia		***Hyponatremia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Back pain		***Back pain (Gr 3)***
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Neuralgia		***Neuralgia (Gr 2)***
		Peripheral motor neuropathy	
	Peripheral sensory neuropathy[6]		***Peripheral sensory neuropathy[6] (Gr 3)***
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
	Proteinuria		***Proteinuria (Gr 2)***
		Renal and urinary disorders - Other (atonic urinary bladder)[6]	
	Urinary retention[6]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Bronchial obstruction		
Cough			***Cough (Gr 3)***
	Dyspnea		***Dyspnea (Gr 3)***
	Hypoxia		***Hypoxia (Gr 3)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		***Pruritus (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 3)***
VASCULAR DISORDERS			
	Capillary leak syndrome		***Capillary leak syndrome (Gr 3)***
	Hypertension		
	Hypotension		***Hypotension (Gr 3)***

[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]There have been rare instances of atypical hemolytic uremic syndrome in the absence of documented infection and resulting in renal insufficiency, electrolyte abnormalities, anemia, and hypertension.

[3]Neurological disorders of the eye including blurred vision, diplopia, cycloplegia, mydriasis, photophobia, optic nerve disorder, eyelid

ptosis, and fixed pupils have been observed.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[5]Myelitis expressed as transverse myelitis has occurred in patients treated with chimeric MoAb 14.18. Symptoms may include weakness, paresthesia, sensory loss, or incontinence.

[6]Acute urinary retention occurs during therapy and is thought to be due to fluid shifts and narcotic administration that accompany ch14.18 administration. Atonic urinary bladder results in chronic urinary retention (CUR) that requires intermittent urethral catheterization days to weeks following chimeric MoAb 14.18 administration.

Adverse events reported on MoAb 14.18, chimeric (CH14.18) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MoAb 14.18, chimeric (CH14.18) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (thrombotic microangiopathy [e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]); Bone marrow hypocellular; Febrile neutropenia; Hemolysis
CARDIAC DISORDERS - Cardiac disorders - Other (gallop on exam); Cardiac disorders - Other (N-terminal BNP); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Mobitz (type) II atrioventricular block; Myocardial infarction; Palpitations; Pericardial effusion; Supraventricular tachycardia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Ear pain; Hearing impaired
ENDOCRINE DISORDERS - Endocrine disorders - Other (transient hypoaldosteronism); Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Papilledema; Periorbital edema; Scleral disorder
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Cheilitis; Colitis; Constipation; Duodenal obstruction; Dysphagia; Enterocolitis; Esophageal stenosis; Esophageal ulcer; Esophagitis; Gastrointestinal disorders - Other (bleeding, NOS); Gastrointestinal disorders - Other (esophageal stricture); Gastrointestinal disorders - Other (ischemic bowel); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastroparesis; Hemorrhoidal hemorrhage; Ileus; Intra-abdominal hemorrhage; Lower gastrointestinal hemorrhage; Mucositis oral; Oral pain; Rectal hemorrhage; Stomach pain; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema face; Edema trunk; Fatigue; General disorders and administration site conditions - Other (cold and clammy); General disorders and administration site conditions - Other (vascular leak syndrome); Hypothermia; Injection site reaction; Localized edema; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (cholestasis)
IMMUNE SYSTEM DISORDERS - Cytokine release syndrome
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alkaline phosphatase increased; Blood bilirubin increased; Cardiac troponin I increased; Cholesterol high; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Fibrinogen decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count increased; Urine output decreased; Weight gain; Weight loss
METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration; Hypercalcemia; Hyperglycemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hypoglycemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Bone pain; Chest wall pain; Muscle weakness lower limb; Myalgia; Neck pain
NERVOUS SYSTEM DISORDERS - Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Headache; Hydrocephalus; Meningismus; Movements involuntary; Nystagmus; Oculomotor nerve disorder; Paresthesia; Seizure; Somnolence; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Delirium; Hallucinations; Insomnia; Irritability; Personality change; Restlessness
RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Glucosuria; Hematuria; Renal and urinary disorders - Other (acute renal insufficiency); Renal and urinary disorders - Other (urethritis); Renal hemorrhage
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Hematosalpinx; Ovarian hemorrhage; Pelvic pain; Penile pain; Prostatic hemorrhage; Spermatic cord hemorrhage; Testicular hemorrhage; Uterine hemorrhage; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Apnea; Atelectasis; Bronchospasm; Laryngeal edema; Laryngopharyngeal dysesthesia; Laryngospasm; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumonitis; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (tachypnea);

Stridor; Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Erythema multiforme; Hyperhidrosis
VASCULAR DISORDERS - Flushing

Note: Dinutuximab (MoAb 14.18, chimeric) 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.

Magrolimab activates macrophages as does dinutuximab. Given that dinutuximab causes pain due to GD2 expression on normal nerve cells, there is a theoretical potential for worsening of this pain or other neurologic toxicity such as motor dysfunction or permanent damage to peripheral nerve cells.

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.
  - Other AEs for the protocol that do not require expedited reporting are outlined in Section 10.3.4, if any exist.

- **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 Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period and used to collect AEs that start during the period or persist from the previous reporting period. The Clinical Research Associate (CRA) will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Event form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

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 (fields added to the form during study build do not need to be query-free for the integration call with CTEP-AERS to be a success).

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. 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.

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 deep link from Medidata Rave.
Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents > Education and Promotion, and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information > User Guides.

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. 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

10.4 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/screening evaluations are to be conducted within 4 weeks (28 days) prior to start of protocol therapy. Scans must be done <4 weeks (28 days) prior to the start of protocol 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.

DOSE FINDING (ARM A): Priming, Safety Lead-In and Treatment Cycles[1]

Treatment Cycles/Visits	Screening	Treatment								Follow Up		
		Week 1	Safety Lead-In	Cycle 1			Cycle 2 and subsequent cycles			End of Therapy	Safety	Follow Up[17]
		Priming	Week 2-3	Week 1		Weeks 2-3	Week 1		Weeks 2-3[20]			
Scheduling Window	Within 28 days	Day 1	Day 1 ±1 day	Day 1 ±2 days	Day 2-5 ±2 days	Day 1 ±2 days	Day 1 ±2 days	Day 2-5 ±2 days	Day 1 ±2 days	Within 10 days after last IP dose	30 days after last IP dose ±7 days	Month 2, 4, 6, 9, 12 and annually (Year 2-5)
Administrative Procedures												
Informed consent/assent	X											
Eligibility evaluation	X											
Medical history[2]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[3]	X	X	X	X	X	X	X	X	X	X	X	
Treatment												
Hu5F9-G4 (magrolimab) administration[4]		X	X	X		X	X		X[4]			
Dinutuximab administration[5]					X			X				
Clinical Assessments												
Height, weight[6]	X	X		X			X			X	X	
Physical exam[7]	X	X	X	X			X			X	X	X
Vital signs[8]	X	X	X	X	X	X	X	X	X	X	X	
ECG	X											
ECHO, MUGA or Cardiac MRI	X											
Performance status[9]	X	X		X			X				X	
Disease evaluation[10]	X			End of Cycle 2 and 4, and then after every 4 cycles								X
Confirmatory imaging[11]		As per **Section** Error! Reference source not found.										

DOSE FINDING (ARM A): Priming, Safety Lead-In and Treatment Cycles[1]

Treatment Cycles/Visits	Screening	Treatment								Follow Up		
		Week 1	Safety Lead-In	Cycle 1			Cycle 2 and subsequent cycles			End of Therapy	Safety	Follow Up[17]
		Priming	Week 2-3	Week 1		Weeks 2-3	Week 1		Weeks 2-3[20]			
Scheduling Window	Within 28 days	Day 1	Day 1 ±1 day	Day 1 ±2 days	Day 2-5 ±2 days	Day 1 ±2 days	Day 1 ±2 days	Day 2-5 ±2 days	Day 1 ±2 days	Within 10 days after last IP dose	30 days after last IP dose ±7 days	Month 2, 4, 6, 9, 12 and annually (Year 2-5)
Bone marrow aspiration and biopsy if NBL/ ganglioneuroblastoma[10, 21]	X ----------→			End of Cycle 2 and 4, and then after every 4 cycles								X
AE and SAE evaluation[12]		Continuously										
Clinical Laboratory Tests[13]												
Pregnancy test[14]	X	As required locally										
CBC with differential and platelets	X	X[22]	X[22]	X			X				X	
Electrolytes, creatinine, urea (BUN), Ca^{2+}, PO_4^{3-}, Mg^{2+}	X	X	X	X			X				X	
ALT, AST, bilirubin	X	X		X			X				X	
Amylase, lipase, CRP	X	X		X			X				X	
Blood cell ABO phenotyping (minor antigens)[15]	X ----------→											
Type and screen (ABO/rhesus) [15]	X ----------→											
Direct Antiglobulin Test (DAT) [direct Coombs test][15]	X ----------→											
Urinalysis	X											
Correlative Exploratory Biology Studies												
Tumor tissue specimen[19]		X	X - As available									
Blood samples[18]		X	X	X	X	X	X	X	X	X		
Bone marrow aspirate[21]	X ----------→						End of Cycle 2, 4, 8 and 12			X		

[1] Arm A included the priming dose plus single agent Safety Lead-In conducted over 21 days, then treatment cycles (21-day cycle) begin. Cycles may be repeated as long as the patient does not have unacceptable toxicity (see **Section 6.3** or **Section** Error! Reference source not found.) or disease progression to a maximum of 12 cycles.

[2] Standard medical history is acceptable. Following screening, updates to medical history should be recorded.

[3] Prior and concomitant medications – All medications taken within 21 days prior to treatment initiation and all new medications, including all medications for AEs, taken up to 30 days after treatment discontinuation should be recorded.

[4] Hu5F9-G4 (magrolimab) will be administered as a priming dose, single agent Safety Lead-In and Day 1 of every week of every 3 week Cycles as outlined in **Section 6.2**. A premedication regimen (oral acetaminophen and diphenhydramine, or comparable regimen) is required before the initial doses of Hu5F9-G4 (magrolimab) and in case of re-priming of the patient after > 4 weeks interruption in treatment.

[5] Dinutuximab will be administered on Days 2-5 during the first week of every cycle as specified in **Section 6.2.** Administer antihistamines, antipyretics (i.e., acetaminophen and ibuprofen) and analgesia prior to each dinutuximab infusion as per **Section 6.2**.

[6] Both height and weight will be recorded at screening. Only weight will be recorded at subsequent applicable visits.

[7] A complete physical examination as well as a cancer-specific physical exam will be performed at screening. Physical exams at subsequent applicable visits will be targeted based on the investigator's clinical observations and symptomatology. If a physical exam is performed within 3 days prior to a subsequent dosing day it does not need to be repeated on the dosing day provided there is no new status change.

[8] Vital signs = heart rate, respiratory rate, blood pressure, temperature, pulse oximetry. See Section 6.2.1.3 and 6.2.1.4 for collection timepoints during and after infusion. Vital signs must also be collected at each non-dosing visit.

[9] Karnofsky score of ≥50% is required for patients >16 years, and Lansky score of ≥50% is required for patients ≤16 years. Patients unable to walk due to paralysis, but who are using a wheelchair, will be considered ambulatory for the purpose of assessing the performance score. See APPENDIX A.

[10] Baseline disease evaluation will occur within 28 days of treatment initiation. During the treatment period Cycles 1 through 4, patients should be re-evaluated for response at the end of Cycles 2 and 4. After Cycle 4, disease evaluation will occur every 12 weeks (after every 4 cycles). Disease evaluations should occur within 7 days prior to dosing of the subsequent cycle. If treatment is delayed, disease evaluations will follow the originally scheduled calendar dates and should not be adjusted for the dose delay. The same method of assessment and technique should be used throughout the study. See Section 12 for disease parameters, methods of assessment, and response criteria. For patients with neuroblastoma/ganglioneuroblastoma, bilateral bone marrow aspirates and trephine biopsies are required at all disease assessment time points (see Section 12.2) and Follow-up Visits for disease evaluation.

[11] Confirmatory scans should also be performed according to Section 12 in patients with measurable disease. The same method of assessment and technique should be used throughout the study.

[12] All AEs occurring within 30 days after the last dose of the study drug must be reported in a routine manner using Rave. Additionally, all AEs that occur within 30 days after the last dose of the study drug, regardless of causality, meeting the expedited reporting criteria outlined in Section 10.3 must also be reported expeditiously via CTEP-AERS.

[13] All clinical laboratory tests must be performed in a licensed laboratory according to local policy. Pregnancy tests may be performed at the site using a licensed test. Laboratory results outside the limits of eligibility may be repeated to confirm eligibility and must be within the limits of eligibility before treatment initiation. Clinical laboratory tests conducted during screening do not need to be repeated on C1D1 if completed within 7 days prior to treatment initiation. All clinical laboratory tests during the treatment period must be performed within 72 hours prior to dosing. If treatment is delayed all clinical laboratory tests (and their respective windows) will adjust with the dose delay to reflect the patient's clinical status at the time of dosing.

[14] Females of childbearing potential must have a negative urine or serum pregnancy test within 30 days of enrollment and within 72 hours prior to treatment initiation. Additional pregnancy tests (serum or urine) should be obtained throughout the study in accordance with local policy.

[15] Specimen **must** be drawn, completed, resulted and active per institutional guidelines prior to the Priming dose of Hu5F9-G4 (magrolimab). ABO, Rh, and DAT may be pan-reactive due to Hu5F9-G4 (magrolimab) binding to red cells (see Section 7.2.4).

[17] Upon treatment discontinuation, patients will complete the Safety Visit within 30 (±7) days, and Follow-up Visits at month 2 (± 1 week), month 4 (± 2 weeks), month 6 (± 4 weeks), month 9 (± 4 weeks), and month 12 (± 2 months) and then yearly (± 2 months) until year 5, or until disease progression or until death, lost to follow-up, withdrawal of consent, or the end of the study, whichever occurs first. If a subsequent anti-cancer therapy is to be administered after treatment discontinuation but before the scheduled Safety Visit, the Safety Visit assessments should be conducted prior to the start of the new therapy if possible.

- Follow-up Visits will be completed in-person unless the patient does not agree to continue in-person visits. In this case telephone contact may be arranged to ensure the collection of as many safety and efficacy parameters as possible. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.
- Patients removed from protocol therapy for unacceptable AE(s) will be followed until resolution or stabilization of the AE. In addition, these patients will complete the EOT, Safety, and Follow-up Visits according to protocol.

[18] All blood draws for correlative exploratory biology studies will be performed according to the schedule outlined in Table 3, Specimen Collection Schedule; and Section 5. All blood draws for correlative exploratory biology studies must be performed prior to dosing. If treatment is delayed, blood draws for correlative exploratory biology studies will follow the originally scheduled calendar dates and should not be adjusted for the dose delay.

[19] Archival slides will be requested from all patients. If available, clinical biopsies or surgical samples obtained during treatment or at disease progression will be requested.

[20] After Cycle 2, Hu5F9-G4 (magrolimab) will be administered ONLY on Day 1 of week 1 and 3 only (week 2 will be a week of rest).

[21] Bone marrow aspirations will be conducted in all patients with neuroblastoma/ganglioneuroblastoma (as per INRC). Week 1, Day 1 collection is mandatory, *except* if viably frozen bone marrow aspirate collected within 4 weeks (28 days) of the Priming dose (Week 1, Day 1) is available and can be provided to the EET Biobank. Bone marrow aspirates are required at all disease assessment timepoints (end of Cycle 2, 4, 8 and 12). Bone marrow aspirate at End of Therapy is optional.

[22] Within 24 hours prior to the Priming dose (Week 1) of Hu5F9-G4, hemoglobin must be ≥ 9.5 g/dL. Within 24 hours prior to the first full dose (Week 2) of Hu5F9-G4, hemoglobin must be ≥ 9.0 g/dL (see Section 6.2.1.3). Hemoglobin must be checked 3 to 6 hours after the initiation of the first and second doses of Hu5F9-G4 (magrolimab).

Baseline/screening evaluations are to be conducted within 4 weeks (28 days) prior to start of protocol therapy. Scans must be done < 4 weeks (28 days) prior to the start of protocol 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.

EXPANSION COHORTS (ARM B) – Priming and Treatment Cycles[1]

Treatment Cycles/Visits	Screening	Treatment							Follow Up		
		Priming	Cycle 1			Cycle 2 and subsequent cycles			End of Therapy	Safety	Follow Up[17]
		Week 1	Week 2		Weeks 3-4	Week 1		Weeks 2-3[20]			
Scheduling Window	Within 28 days	Day 1	Day 1 ±2 days	Day 2-5 ±2 days	Day 1 ±2 days	Day 1 ±2 days	Day 2-5 ±2 days	Day 1 ±2 days	Within 10 days after last IP dose	30 days after last IP dose ±7 days	Month 2, 4, 6, 9, 12 and annually (Year 2-5)
Administrative Procedures											
Informed consent/assent	X										
Eligibility evaluation	X										
Medical history[2]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[3]	X	X	X	X	X	X	X	X	X	X	X
Treatment											
Hu5F9-G4 (magrolimab) administration[4]		X	X		X	X		X[20]			
Dinutuximab administration[5]				X			X				
Clinical Assessments											
Height, weight[6]	X	X	X			X			X	X	X
Physical exam[7]	X	X	X			X			X	X	X
Vital signs[8]	X	X	X	X	X	X	X	X	X	X	X
ECG	X										
ECHO, MUGA or Cardiac MRI	X										
Performance status[9]	X	X	X			X				X	X
Disease evaluation[10]	X		End of Cycle 2 and 4, and then after every 4 cycles								X
Confirmatory imaging[11]		As per **Section** Error! Reference source not found.									
Bone marrow aspiration and biopsy if NBL/ganglioneuroblastoma [10, 21]	X ----------→	End of Cycle 2 and 4, and then after every 4 cycles									X
AE and SAE evaluation[12]		Continuously									
Clinical Laboratory Tests[13]											

EXPANSION COHORTS (ARM B) – Priming and Treatment Cycles[1]											
Treatment Cycles/Visits	**Screening**	**Treatment**							**Follow Up**		
		Priming	**Cycle 1**			**Cycle 2 and subsequent cycles**			**End of Therapy**	**Safety**	**Follow Up[17]**
		Week 1	**Week 2**		**Weeks 3-4**	**Week 1**		**Weeks 2-3[20]**			
Scheduling Window	Within 28 days	Day 1	Day 1 ±2 days	Day 2-5 ±2 days	Day 1 ±2 days	Day 1 ±2 days	Day 2-5 ±2 days	Day 1 ±2 days	Within 10 days after last IP dose	30 days after last IP dose ±7 days	Month 2, 4, 6, 9, 12 and annually (Year 2-5)
Pregnancy test[14]	X	As required locally									
CBC with differential and platelets	X	X[22]	X[22]			X				X	
Electrolytes, creatinine, urea (BUN), Ca^{2+}, PO_4^{3-}, Mg^{2+}	X	X	X			X				X	
ALT, AST, bilirubin	X	X	X			X				X	
Amylase, lipase, CRP	X	X	X			X					
Blood cell ABO phenotyping (minor antigens)[15]	X ----------→										
Type and screen (ABO/rhesus)[15]	X ----------→										
Direct Antiglobulin Test (DAT) [direct Coombs test]	X ----------→										
Urinalysis	X										
Correlative Exploratory Biology Studies											
Tumor tissue specimen[19]	X	X - As available									
Blood samples[18]		X	X	X	X	X	X	X	X		
Bone marrow aspirate[21]	X ----------→					End of Cycle 2, 4, 8 and 12			X		

1 Arm B patients will receive the priming dose followed by Cycle 1 and 2 (each 21 days). Cycles may be repeated as long as the patient does not have unacceptable toxicity (see **Section 6.3** or **Section** Error! Reference source not found.) or disease progression to a maximum of 12 cycles for patients in cohorts B1, B2 and B3 and to a maximum of 5 cycles post resection for patients in cohort B4.

2 Standard medical history is acceptable. Following screening, updates to medical history should be recorded.

3 Prior and concomitant medications – All medications taken within 21 days prior to treatment initiation and all new medications, including all medications for AEs, taken up to 30 days after treatment discontinuation should be recorded.

4 Hu5F9-G4 (magrolimab) will be administered as a priming dose, single agent Safety Lead-In and Day 1 of every week of every 3 week Cycles as outlined in **Section 6.2**. A premedication regimen (oral acetaminophen and diphenhydramine, or comparable regimen) is required before the initial doses of Hu5F9-G4 (magrolimab) and in case of re-priming of the patient after > 4 weeks interruption in treatment.

[5] Dinutuximab will be administered on Days 2-5 during the first week of every cycle as specified in **Section 6.2**. Administer antihistamines, antipyretics (i.e. acetaminophen and ibuprofen) and analgesia prior to each dinutuximab infusion as per **Section 6.2**.

[6] Both height and weight will be recorded at screening. Only weight will be recorded at subsequent applicable visits.

[7] A complete physical examination as well as a cancer-specific physical exam will be performed at screening. Physical exams at subsequent applicable visits will be targeted based on the investigator's clinical observations and symptomatology. If a physical exam is performed within 3 days prior to a subsequent dosing day it does not need to be repeated on the dosing day provided there is no new status change.

[8] Vital signs = heart rate, respiratory rate, blood pressure, temperature, pulse oximetry. See Sections 6.2.1.3 and 6.2.1.4 for collection timepoints during and after infusion. Vital signs must also be collected at each non-dosing visit.

[9] Karnofsky score of ≥50% is required for patients >16 years, and Lansky score of ≥50% is required for patients ≤16 years. Patients unable to walk due to paralysis, but who are using a wheelchair, will be considered ambulatory for the purpose of assessing the performance score. See APPENDIX A.

[10] Baseline disease evaluation will occur within 28 days of treatment initiation. During the treatment period Cycles 1 through 4, patients in Cohorts B1, B2 and B3 should be re-evaluated for response at the end of Cycles 2 and 4. After Cycle 4, disease evaluation will occur every 12 weeks (after every 4 cycles). Disease evaluations should occur within 7 days prior to dosing of the subsequent cycle. If treatment is delayed, disease evaluations will follow the originally scheduled calendar dates and should not be adjusted for the dose delay. The same method of assessment and technique should be used throughout the study. See Section 12 for disease parameters, methods of assessment, and response criteria. Cohort B4 – refer to Section 12 for disease evaluation timepoints. For patients with neuroblastoma/ganglioneuroblastoma, bilateral bone marrow aspirates and trephine biopsies are required at all disease assessment time points (see Section 12.2) and Follow-up Visits for disease evaluation.

[11] Confirmatory scans should also be performed according to Section 12 in patients with measurable disease. The same method of assessment and technique should be used throughout the study.

[12] All AEs occurring within 30 days after the last dose of the study drug must be reported in a routine manner using Rave. Additionally, all AEs that occur within 30 days after the last dose of the study drug, regardless of causality, meeting the expedited reporting criteria outlined in Section 10.3 must also be reported expeditiously via CTEP-AERS.

[13] All clinical laboratory tests must be performed in a licensed laboratory according to local policy. Pregnancy tests may be performed at the site using a licensed test. Laboratory results outside the limits of eligibility may be repeated to confirm eligibility and must be within the limits of eligibility before treatment initiation. Clinical laboratory tests conducted during screening do not need to be repeated on C1D1 if completed within 7 days prior to treatment initiation. All clinical laboratory tests during the treatment period must be performed within 72 hours prior to dosing. If treatment is delayed all clinical laboratory tests (and their respective windows) will adjust with the dose delay to reflect the patient's clinical status at the time of dosing.

[14] Females of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to treatment initiation. Additional pregnancy tests (serum or urine) should be obtained throughout the study in accordance with local policy.

[15.] Specimen **must** be drawn, completed, resulted and active per institutional guidelines prior to the Priming dose of Hu5F9-G4 (magrolimab). ABO, Rh, and DAT may be pan-reactive due to Hu5F9-G4 (magrolimab) binding to red cells (see Section 7.2.4).

[17] Upon treatment discontinuation, patients will complete the Safety Visit within 30 (±7) days, and Follow-up Visits at month 2 (± 1 week), month 4 (± 2 weeks), month 6 (± 4 weeks), month 9 (± 4 weeks), and month 12 (± 2 months) and then yearly (± 2 months) until year 5, or until disease progression or until death, lost to follow-up, withdrawal of consent, or the end of the study, whichever occurs first. If a subsequent anti-cancer therapy is to be administered after treatment discontinuation but before the scheduled Safety Visit, the Safety Visit assessments should be conducted prior to the start of the new therapy if possible.

- Follow-up Visits will be completed in-person unless the patient does not agree to continue in-person visits. In this case telephone contact may be arranged to ensure the collection of as many safety and efficacy parameters as possible. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

- Patients removed from protocol therapy for unacceptable AE(s) will be followed until resolution or stabilization of the AE. In addition, these patients will complete the EOT, Safety, and Follow-up Visits according to protocol.

[18] All blood draws for correlative exploratory biology studies will be performed according to the schedule outlined in Table 3, Specimen Collection Schedule; and Section 5. All blood draws for correlative exploratory biology studies must be performed prior to dosing. If treatment is delayed, blood draws for correlative exploratory biology studies will follow the originally scheduled calendar dates and should not be adjusted for the dose delay.

[19] Archival slides will be requested from all patients. If available, clinical biopsies or surgical samples obtained during treatment or at disease progression will be requested. Cohort B4 - Pulmonary metastases resected from staged resection at enrollment and then after one cycle of protocol therapy OR if only one resection performed, tissue will be requested at enrollment after surgical metastasectomy.

[20] After Cycle 2, Hu5F9-G4 (magrolimab) will be administered ONLY on Day 1 of week 1 and week 3 (week 2 will be a week of rest).

[21] Bone marrow aspirations will be conducted in all patients with neuroblastoma (as per INRC). Week 1, Day 1 collection is mandatory, *except* if viably frozen bone marrow aspirate collected within 4 weeks (28 days) of the Priming Dose (Week 1, Day 1) is available and can be provided to the EET Biobank. Bone marrow aspirates are required at all disease assessment timepoints (end of Cycle 2, 4, 8 and 12). Bone marrow aspirate at End of Therapy is optional.

[22] Within 24 hours prior to the Priming dose (Week 1) of Hu5F9-G4, hemoglobin must be ≥ 9.5 g/dL. Within 24 hours prior to the first full dose (Week 2) of Hu5F9-G4, hemoglobin must be ≥ 9.0 g/dL (see Section 6.2.1.3). Hemoglobin must be checked 3 to 6 hours after the initiation of the first and second doses of Hu5F9-G4 (magrolimab).

12 EVALUATION CRITERIA

Although the clinical benefit of the combination of Hu5F9-G4 (magrolimab) and dinutuximab 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 as outlined below.

For Arm A and Arm B cohorts 1-3, patients should be evaluated for disease status initially after Cycle 2 and Cycle 4 then after every four cycles of combination therapy, for a maximum of 12 cycles in cohorts 1 through 3. After completion of combination therapy, for patients who have not experienced disease progression, disease evaluations will continue at month 2 (± 1 week), month 4 (± 2 weeks), month 6 (± 4 weeks), month 9 (± 4 weeks), and month 12 (± 2 months) and then every six months (± 2 months) until year 5. Confirmatory scans will also be obtained ≥ 4 weeks following initial documentation of an objective response.

Patients in Arm B cohort 4, who undergo resection of all metastatic lesions (rendered NED) *before* protocol treatment, should be evaluated for disease status after Cycle 2 and after Cycle 5. After Cycle 5 for patients who have not experienced disease progression, disease evaluation will continue at month 2 (± 1 week), month 4 (± 2 weeks), month 6 (± 4 weeks), month 9 (± 4 weeks), and month 12 (± 2 months) and then every six months (± 2 months) until year 5.

Patients in Arm B cohort 4, who undergo staged resection *during* protocol therapy, should be evaluated for baseline disease status after their initial resection (prior to Priming Dose and Cycle 1). The subsequent disease evaluations will be performed following the second surgical resection ***and*** completion of two cycles (i.e., end of Cycle 3), and after five cycles (i.e., end of Cycle 6) of combination therapy. After Cycle 6 for patients who have not experienced disease progression, disease evaluation will continue at month 2 (± 1 week), month 4 (± 2 weeks), month 6 (± 4 weeks), month 9 (± 4 weeks), and month 12 (± 2 months) and then every six months (± 2 months) until year 5.

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks (within 28 days) before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

12.1 Antitumor Effect – Osteosarcoma (Measurable disease)

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1.1 Definitions

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

Evaluable for objective response. Patients must have measurable osteosarcoma at enrollment for the expansion cohort with osteosarcoma (Cohort B3). Those patients who have only received the priming dose and have received at least one dose of Hu5F9-G4 (magrolimab) followed on day 2 by dinutuximab and who do not have their disease

re-evaluated will be considered non-evaluable.

Note: Patients who exhibit disease progression prior to end of Cycle 2 evaluation will be considered evaluable.

12.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm (≥1 cm) with cross sectional imaging (CT scan or MRI), or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.1.3 Methods for Evaluation of Measurable Disease

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the

case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT or MRI scanning in assessment of progression (particularly

possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.1.4 Response Criteria

12.1.4.1 Evaluation of Target Lesions

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

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

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

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

12.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be

representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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

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

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

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

12.2 Response Criteria for Patients with Neuroblastoma (measurable or evaluable disease)

This study will use the revised International Neuroblastoma Response Criteria (INRC) for disease assessment (Park et al., 2017). The updated response criteria incorporate current approaches to imaging of neuroblastoma, including functional imaging. Furthermore, a standardized approach to assessment of bone marrow involvement is included. The current INRC do not include methods of disease assessment that are less sensitive and/or specific for neuroblastoma (^{99}Tc bone scan and catecholamine levels).

12.2.1 Definitions

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

Evaluable for Response: Patients must have evaluable or measurable malignant disease at enrollment for the dose escalation cohorts, and patients enrolling in the expansion cohort with neuroblastoma must have measurable OR MIBG evaluable disease at enrollment. MIBG evaluable disease for eligibility in neuroblastoma is defined as MIBG scan obtained within 3 weeks prior to study entry with positive uptake at a minimum of one site.

Those patients who have only received the priming dose and have received at least one dose of Hu5F9-G4 (magrolimab) followed on day 2 by dinutuximab and who do not have their disease re-evaluated will be considered non-evaluable.

Note: Patients who exhibit disease progression prior to the disease evaluation will also be considered evaluable.

12.2.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with cross sectional imaging (CT scan or MRI), or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will be considered measurable if they demonstrate clear evidence of progression after completion of radiation.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed as per RECIST 1.1 criteria. Patients with neuroblastoma may have conglomerate masses of non-discrete lymph nodes (i.e. multiple contiguous retroperitoneal nodes). When a short axis of a discreet node cannot be identified, a lymph node conglomerate can be measured using the longest diameter of the composite lesion. Tracer avidity of metastatic nodes will be recorded at baseline and during disease evaluations.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. For the purposes of response assessment, target lesions are disease sites that are measurable (non-nodal soft tissue mass ≥ 10 mm in longest dimension or lymph node ≥ 15 mm in short axis) and tracer avid OR are biopsy positive for neuroblastoma or ganglioneuroblastoma. The sum of diameters of target lesions is defined as the sum of the short axis of discrete

lymph nodes (i.e., cervical, axillary nodes) added to the sum of the longest diameters of non-lymph node soft tissue metastases. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Bone lesions: Osteomedullary disease will be assessed using 123I-MIBG scans or FDG-PET scans. Technetium bone scans are no longer used as part of the revised INRC and are not included as part of disease reassessments during this trial. The extent of tracer avid disease will be evaluated using the Curie scoring system. SPECT may be used to confirm the presence or absence of lesions in a given segment of the body. The absolute Curie score should be reported at baseline. A relative score (Curie score at the time of disease assessment divided by baseline Curie score) should be recorded at the time of each disease evaluation.

Bone marrow disease: Bilateral bone marrow aspirates and trephine biopsies are required at disease assessment time points (see **Section 11**). The extent of marrow involvement in all four samples should be recorded. Use of immunohistochemical staining for evaluation of trephine biopsies is strongly encouraged. The percentage of tumor infiltration of bone marrow space assessed by histologic evaluation of trephine/biopsies or counting the number of tumor cells in aspirates by cytology or immunocytology (recommended if available) divided by the number of hematopoietic/mononuclear cells evaluated to obtain a percentage involvement (methodology described by Burchill et al.)(Burchill et al., 2017). The bone marrow sample with the highest percentage of tumor infiltration is used for response assessment. If > 0% to ≤ 5% tumor infiltration is the highest percentage seen among samples obtained, the result should be recorded as minimal marrow disease.

12.2.3 Response Criteria

PRIMARY (SOFT TISSUE) TUMOR RESPONSE[1]

RESPONSE	ANATOMICAL IMAGING & MIBG (FDG-PET[2]) IMAGING
Complete Response (CR)	• < 10 mm residual soft tissue at primary site, AND • Complete resolution of MIBG or FDG-PET[2] uptake (for MIBG non-avid tumors) at primary site
Partial Response (PR)	• ≥ 30% decrease in longest diameter (LD) of primary site • MIBG or FDG-PET[2] uptake at primary site stable, improved or resolved
Progressive Disease (PD)	• 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), AND • a minimum absolute increase of 5 mm in longest dimension[3]
Stable Disease (SD)	• Neither sufficient shrinkage for PR nor sufficient

[1] Not for use in assessment of metastatic sites
[2] For ^{123} I-MIBG non-avid tumors
[3] A mass that has not met PD measurement criteria but has fluctuating ^{123}I-MIBG avidity will not be considered progressive

disease.

RESPONSE AT METASTATIC SOFT TISSUE AND BONE SITES

RESPONSE	ANATOMICAL IMAGING & MIBG (FDG-PET[1]) IMAGING
Complete Response (CR)	Resolution of all sites of disease defined as: • Non-primary target and non-target lesions measure < 10 mm AND • Lymph nodes identified as target lesions decrease to a short axis < 15 mm, AND • MIBG uptake or FDG-PET[1] uptake (for MIBG non-avid tumors) of non-primary lesions resolves completely
Partial Response (PR)	• ≥ 30% decrease in sum of diameters[2] of non-primary target lesions compared to baseline, AND all of the following: o Non-target lesions may be stable or smaller in size AND o No new lesions AND o ≥ 50% reduction in MIBG absolute bone score (Relative MIBG bone score ≥ 0.1 to ≤ 0.5) or ≥ 50% reduction in number of FDG-PET[1] avid bone lesions[3,4]
Progressive Disease (PD)	Any of the following: • Any new soft tissue lesion detected by CT or MRI that is also MIBG avid or FDG-PET avid; • Any new soft tissue lesion seen on anatomic imaging that is biopsied and confirmed to be a neuroblastoma; • Any new bone site that is MIBG avid; • A new bone site that is FDG-PET[1] avid (for MIBG non-avid tumors) AND has CT or MRI findings consistent with tumor OR has been confirmed histologically to be neuroblastoma; • > 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), AND a minimum absolute increase of 5 mm in sum of diameters of target soft tissue lesions; • Relative MIBG score ≥ 1.2[4]
Stable Disease (SD)	Neither sufficient shrinkage for PR nor sufficient increase for PD of non-primary lesions

[1] Used for MIBG non-avid tumors
[2] Sum of diameters is defined as the sum of the short axis of discrete lymph nodes (i.e., cervical, axillary nodes) added to the sum of the longest diameters of non-lymph node soft tissue metastases. Masses of conglomerate non-discrete lymph nodes will be measured using longest diameter.
[3] For patients with soft tissue metastatic disease, resolution of MIBG and/or FDG-PET uptake at the soft tissue sites is not required; all size reduction criteria must be fulfilled.
[4] Relative Curie score is the absolute score for bone lesions at time of response assessment divided by the absolute score for bone lesions at entry onto a clinical trial. MIBG-SPECT or MIBG-SPECT/CT may be used for scoring purposes, but the same imaging methodology should be used for all evaluations.

BONE MARROW RESPONSE

RESPONSE	BONE MARROW STATUS[1]
Complete Response (CR)	Bone marrow with no tumor infiltration upon reassessment, independent of baseline tumor involvement
Progressive Disease (PD)	Any of the following: • Bone marrow without tumor infiltration that becomes > 5% tumor infiltration upon reassessment; or • Bone marrow with tumor infiltration that increases by > 2-fold and has > 20% tumor infiltration upon reassessment.
Minimal Disease (MD)	Any of the following: • Bone marrow with ≤ 5% tumor infiltration and remains > 0-≤ 5% tumor infiltration upon reassessment; or • Bone marrow with no tumor infiltration that becomes ≤ 5% tumor infiltration upon reassessment; or • Bone marrow with >20% tumor infiltration that has > 0-≤ 5% tumor infiltration upon reassessment.
Stable Disease (SD)	Bone marrow with tumor infiltration that remains positive with > 5% tumor infiltration upon reassessment but does not meet CR, MD or PD criteria

[1] Immunohistochemistry strongly encouraged

DETERMINATION OF OVERALL RESPONSE

RESPONSE	CRITERIA
Complete Response (CR)	All components meet criteria for CR
Partial Response (PR)	PR in at least one component and all other components are either CR, MD (Bone marrow), PR (Soft tissue or Bone) or Not involved (NI); no component with PD.
Minor Response (MR)	PR or CR in at least one component but at least one other component with SD; no component with PD.
Stable Disease (SD)	SD in one component with no better than SD or NI in any other component; no component with PD.
Progressive Disease (PD)	Any component with PD

NI = Not involved, site not involved at study entry and remains not involved; MD = Minimal Disease, for bone marrow assessment only.

12.2.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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

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

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 Data and Safety Monitoring Plan

Data and safety is ensured by several integrated components including the Data and Safety Monitoring Committee.

13.1.1 Data and Safety Monitoring Committee

This study will be monitored in accordance with the Children's Oncology Group PEP-CTN policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the COG PEP-CTN Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician external to COG; one external member; one consumer representative; the lead statistician of the PEP-CTN scientific committee; and a member from the NCI. The DSMC meets at least every 6 months to review current study results, as well as data available to the DSMC from other related studies. Approximately 6 weeks before each meeting of the Phase 1 and 2 DSMC, study chairs will be responsible for working with the study statistician to prepare study reports for review by the DSMC. The DSMC will provide recommendations to the PEP-CTN Chair and the Group Chair for each study reviewed to change the study or to continue the study unchanged. Data and Safety Committee reports for institutional review boards can be prepared using the public data monitoring report as posted on the COG member's Web site.

13.1.2 Monitoring by the Study Chair and the Steering Committee

The study chair will monitor the study regularly and enter evaluations of patients' eligibility, evaluability, and dose limiting toxicities into the study database. In addition, study data and the study chair's evaluations will be reviewed by the PEP-CTN Chair, Vice Chair and Statistician on a weekly conference call.

13.2 Data Submission / Data Reporting

Data Mapping Utility (DMU) Reporting Complete

Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Complete reporting consists of Patient Demographics, Baseline Abnormalities, On/Off Treatment/Study Status, Treatment/Course/Dosing information, Adverse Events, Late Adverse Events, and Response data as applicable. More information on the DMU is available on the CTEP Website: https://ctep.cancer.gov/protocolDevelopment/dmu.htm. **DMU reporting is not a responsibility of institutions participating in this trial.**

13.2.1 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. 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 via a direct link available in 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.

Central Monitoring (CM) Review is required for this protocol. CM allows Lead Protocol Organizations (LPOs) to remotely compare data entered in Rave to source documentation to ensure that sites are adhering to the protocol and central monitoring plan as well as accurately transcribing data from patients' charts (i.e., source data verification).

Sites can upload source documents required for CM Review as documented in the central monitoring plan using the Source Document Portal (SDP) application. This application is also available on the CTSU members' website under Auditing & Monitoring and may also be accessed using a direct link within Rave on the CM Alert form. Site staff with any of the Rave roles on a relevant site roster can view and upload source documents. Prior to saving source documents on the SDP, each site is responsible for removing or redacting any Personally Identifiable Information (PII) (note that functionality to do this redaction exists within the SDP itself). Designated LPO staff will review each document after it has been loaded on the SDP to ensure the appropriate documents have been uploaded and to ensure PII is redacted.

Additional information on the SDP is available on the CTSU SDP application under Browser > Document Repository in the Help Topics button or by contacting the CTSU Help Desk (1-888-823-5923 or ctsucontact@westat.com).

13.2.2 Rave-CTEP AERS Integration

The CTEP Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of 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 AE CRF, 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 Agent/Intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rule evaluation process, site staff should verify the following on the AE CRF in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free. *Note:* Fields added to the form during study build do not need to be query free for the integration call with CTEP-AERS to be a success.

The CRA reports AEs in Rave at the time the Site 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 deep link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU member's 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.

13.2.3 Monitoring

On-site, retrospective source data verification is completed by Theradex on an annual basis for 100% of COG PEP-CTN patients enrolled in early phase clinical trials.

This study will additionally include central monitoring as part of data review. Source documents will be uploaded via CTSU's Central Monitoring Portal. (See Appendix W for details.)

13.2.4 Categories of Research Records

Research records for this study can be divided into three categories:

1. Non-computerized Information: Therapy Delivery Maps (TDMs), Pathology Reports, Surgical Reports. These forms are uploaded into RAVE.

2. Reference Labs, Biopathology Reviews, and Imaging Center data: These data accompany submissions to these centers, which forward their data electronically to the PEP-CTN Operations and Data/Statistics Center.

3. Computerized Information Electronically Submitted: All other data will be entered in RAVE with the aid of schedules and worksheets (essentially paper copies of the OPEN and RAVE screens) provided in the case report form (CRF) packet.

See separate CRF Packet, which includes submission schedule.

13.3 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix C.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

13.4 CRADA/CTA/CSA

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 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.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

Performance Status %	Karnofsky Scale (Age >16 years)	Lansky Scale (Age: ≤16 years)	ECOG (Zubrod)	
100	Normal, no complaints, no evidence of disease	Fully active	**0**	Fully Active, able to carry on all pre-disease performance without restrictions.
90	Able to carry on normal activity	Minor restriction in physically strenuous play		
80	Normal activity with effort	Restricted in strenuous play, tires more easily, otherwise active	**1**	Restricted in physically strenuous activity but ambulatory, able to carry out light or sedentary work, e.g. light housework, office work.
70	Cares for self, unable to carry on normal activity or to do active work	Both greater restrictions of, and less time spent in active play		
60	Requires occasional assistance but is able to care for most needs	Ambulatory up to 50% of time, limited active play with assistance/supervision	**2**	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Requires considerable assistance and frequent medical care	Considerable assistance required for any active play, fully able to engage in quiet play		
40	Disabled, requires special care and assistance	Able to initiate quite activities	**3**	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated, although death not imminent	Needs considerable assistance for quiet activity		
20	Very sick, hospitalization necessary	Limited to very passive activity initiated by others (*e.g.,* TV)	**4**	Completely disabled. Cannot carry out any self-care. Totally confined to a bed or chair.
10	Moribund, fatal process progressing rapidly	Completely disabled, not even passive play		

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 glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey *et al.*, 2009).

Formulae:

Race and Sex	Serum Creatinine (SCr), *µmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$

SCr in mg/dL; Output is in mL/min/1.73 m^2 and needs no further conversions.

2. eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al*., 2006).

$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if black)
Output is in mL/min/1.73 m^2 and needs no further conversions.

3. 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. Levey, A.S., L.A. Stevens, C.H. Schmid, *et al*. (2009). A new equation to estimate glomerular filtration rate. *Ann Inter Med*. 150:604-612.
2. Levey, A.S., J. Coresh, T. Greene, *et al*. (2006). Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 145:247-254.
3. Cockcroft, D.W. and M.H. Gault. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*. 16:31-41.

APPENDIX C: CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP-sponsored research protocol, then the guidelines below must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, *etc.*, available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.

- Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
- Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX D: PRE-BIOPSY ASSESSMENT

A pre-biopsy lesion assessment can increase trial safety and efficiency. By agreement between all investigators, an attempt at biopsy will be made if the clinical trial team determines that a biopsy poses minimal relative risk, provides potential clinical gain to the participant, and will likely yield sufficient tissue for analysis.

Pre-biopsy assessments will be reported and tracked through a trial-specific CRF within the CTEP Medidata Rave system. Additional information can be found in the Investigational Radiology SOP available at: https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_IR_Research_Biopsy_SOP.pdf.

Individual Patient Pre-Biopsy Assessment

IR co-investigators are encouraged to apply this pre-biopsy scoring and correlation system to assist in the determination of biopsy appropriateness.

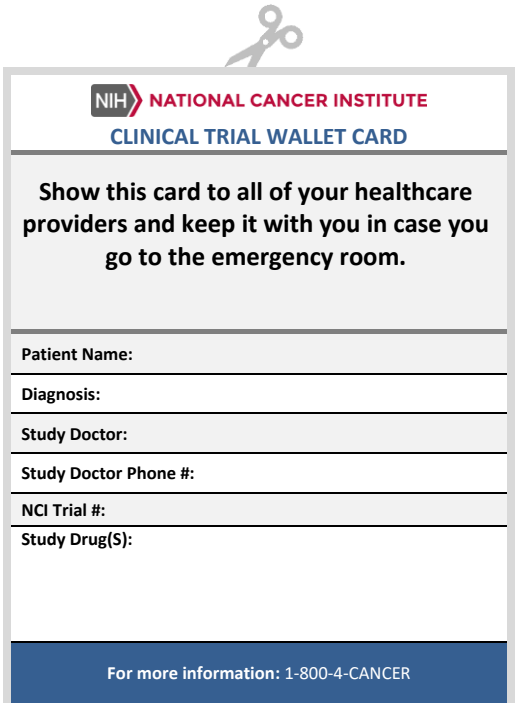
IR co-investigators assign a subjective score of 1-3 based on likelihood of success due to lesion characteristics.

1. Biopsy should not be done
    a) Due to safety concerns
    b) Due to lack of suitable lesion for biopsy

2. Uncertainty about success
    a) Due to access path to lesion
    b) Due to lesion characteristics

3. Likely successful
    - Lesion characteristics to be considered
    - Size (small) (<2 cm)
    - Location/path to lesion
    - Morphologic features (necrosis, sub-solid, sclerosis, ill-defined/infiltrative)
    - PET (+/-), avidity
    - Organ/site (sclerotic bone is low yield; fine needle aspiration to be used)

APPENDIX E: 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:
Study Doctor:
Study Doctor Phone #:
NCI Trial #:
Study Drug(S):

For more information: 1-800-4-CANCER

APPENDIX F: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY PED-CITN-03
(for children from 7 through 13 years of age)

We want to tell you all about this study. You and your family can decide if you want to be in it. Ask questions if you don't understand.

1. What is the name of the study? Testing the combination of two immunotherapy drugs (magrolimab and dinutuximab) in children, adolescents, and young adults with relapsed/refractory neuroblastoma or relapsed osteosarcoma

2. Who is in charge of the study? The study is being done by PEP-CTN and is being done at other hospitals.

3. What is this study about? We are asking you to take part in a research study because you have osteosarcoma or neuroblastoma that has come back or has not gotten better with other treatments. Osteosarcoma is a type of bone cancer. Neuroblastoma is a type of cancer that grows in several areas of the body, including the abdomen and in the chest, neck, and near the spine. After doing tests, we have found that you have one of these types of cancer. A research study is when doctors work together to try out new ways to help people who are sick. We will still take care of you no matter what you decide.

   This study is testing two immune drugs called Hu5F9-G4 (or magrolimab) and dinutuximab in people with cancer like you. Doctors want to see what effects (both good and bad) these drugs have on people and their cancer.

4. What will happen to me in this study? Children who are part of this study will go to the study doctor's office every week for about 8-9 weeks and then every other week, to be given the magrolimab. Every 3 weeks, starting with Cycle 1, you will stay in the hospital for about 4 days and be given the dinutuximab. You will get the research drugs for about 9 months if they make your cancer better or if your cancer does not get worse.You will have some tests and check-ups done more often than if you weren't part of this study. Some of these tests will require extra needle sticks for blood collection. We will follow your health after you finish the study treatment.

   The following would be done at the study visits:

   - You will be asked questions about your health and look at your past doctor visits and use information about your care.
   - We will take some blood by putting a needle in your arm. This blood will be used for research tests and to monitor your safety and health. The blood will be taken when you first join the study, while you are taking the research drugs, and when you stop taking the research drugs.
   - We will check your temperature, breathing, and heartbeat at most visits.
   - A doctor or a nurse will give you the research drugs with a needle in your arm.
   - Scans or exams of your body will be done to learn more about your cancer.

- When you first join this study, we will do research tests on a piece of your cancer. This piece may be left over from a test or surgery you already had for your cancer care or a new piece from a test or surgery if you have this before you start taking the research drugs.

If you have a test or surgery for your cancer care after you start taking the research drugs, we will take a piece of your cancer from this procedure and do research tests on it as well. The tests on your cancer pieces and bone marrow are to learn how magrolimab and dinutuximab can be used to help other children with cancer like you. You and your study doctor will not receive the results of these tests.

Sometimes good things can happen to people when they are in a research study. These good things are called "benefits".We hope that a benefit to you of being part of this study is a better chance at getting rid of your neuroblastoma or osteosarcoma, but we don't know for sure if there is any benefit of being part of this study.

Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks". The risks to you from this study are:

- The needle that we use to take your blood may hurt. Sometimes the needle can leave a bruise on the skin. We can put a cream on your skin before we take blood. This cream will numb your skin so the needle won't hurt as much. If you have a catheter (plastic tube) put in a large vein, your blood may be taken through this catheter, so we won't have to put in a needle to take your blood. This catheter may also be used to give you medicines.

- The study drugs can make you feel hot or cold, sick to your stomach, head hurt, and more tired than usual. You could also get a rash or cough.

- The study drugs can make you feel strange or different. You must tell your parents and the study doctor if you feel sick when taking the study drugs.

- You may not be able to go to school or play or take part in activities for a little while.

- Other things may happen to you that we don't yet know about. You can say 'no' to what we ask you to do for the research at any time and we will stop.

5. Do I have to be in the study? Your family can choose to be part of this study or not. You and your family can also decide to stop being in this study at any time once you start. The doctors and nurses will still take care of you. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

6. We are asking your permission to collect additional tumor tissue, bone marrow, and blood samples. We want to see if there are ways to tell how the cancer will respond to treatment. The tumor tissue and bone marrow samples will be taken at the same time as for your other procedures, so there would be no extra procedures. The blood samples will be taken at the same times that blood is collected for your other procedures so there will be no extra needle sticks. You can still take part in this study even if you don't allow us to collect extra tumor tissue, bone marrow, or blood samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY PED-CITN-03
(for teens from 14 through 17 years of age)

We want to tell you all about this study. You and your family can decide if you want to be in it. Ask questions if you don't understand.

1. What is the name of the study? Testing the combination of two immunotherapy drugs (magrolimab and dinutuximab) in children, adolescent, and young adults with relapsed/refractory neuroblastoma or relapsed osteosarcoma

2. Who is in charge of the study? The study is being done by PEP-CTN and is being done at other hospitals.

3. What is this study about? We are asking you to take part in a research study because you have osteosarcoma or neuroblastoma that has come back or has not gotten better with other treatments. Osteosarcoma is a type of bone cancer. Neuroblastoma is a type of cancer that grows in several areas of the body, including the abdomen and in the chest, neck, and near the spine. After doing tests, we have found that you have one of these types of cancer. A research study is when doctors work together to try out new ways to help people who are sick. We will still take care of you no matter what you decide.

   This study is testing two immune drugs called Hu5F9-G4 (or magrolimab) and dinutuximab in people with cancer like you. Doctors want to see what effects (both good and bad) these drugs have on people and their cancer.

4. What will happen to me in this study? Children who are part of this study will go to the study doctor's office every week for about 8-9 weeks and then every other week, to be given the magrolimab. Every 3 weeks, starting with Cycle 1, you will stay in the hospital for about 4 days and be given the dinutuximab. You will get the research drugs for about 9 months if they make your cancer better or if your cancer does not get worse. You will have some tests and check-ups done more often than if you weren't part of this study. Some of these tests will require extra needle sticks for blood collection. We will follow your health after you finish the study treatment.

   The following would be done at the study visits:

   - You will be asked questions about your health and look at your past doctor visits and use information about your care.

   - We will take some blood by putting a needle in your arm. This blood will be used for research tests and to monitor your safety and health. The blood will be taken when you first join the study, while you are taking the research drugs, and when you stop taking the research drugs.

   - We will check your temperature, breathing, and heartbeat at most visits.

   - A doctor or a nurse will give you the research drugs with a needle in your arm.

   - Scans or exams of your body will be done to learn more about your cancer.

   - When you first join this study, we will do research tests on a piece of your cancer. This piece may be left over from a test or surgery you already had for your cancer care or a new piece from a test or surgery if you have this before you start taking the research drugs.

If you have a test or surgery for your cancer care after you start taking the research drugs, we will take a piece of your cancer from this procedure and do research tests on it as well. The tests on your cancer pieces and bone marrow are to learn how magrolimab and dinutuximab can be used to help other children with cancer like you. You and your study doctor will not receive the results of these tests.

Sometimes good things can happen to people when they are in a research study. These good things are called "benefits". We hope that a benefit to you of being part of this study is a better chance at getting rid of your neuroblastoma or osteosarcoma, but we don't know for sure if there is any benefit of being part of this study.

Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks". The risks to you from this study are:

- The needle that we use to take your blood may hurt. Sometimes the needle can leave a bruise on the skin. We can put a cream on your skin before we take blood. This cream will numb your skin so the needle won't hurt as much. If you have a catheter (plastic tube) put in a large vein, your blood may be taken through this catheter, so we won't have to put in a needle to take your blood. This catheter may also be used to give you medicines.

- The study drugs can make you feel hot or cold, sick to your stomach, head hurt, and more tired than usual. You could also get a rash or cough.

- The study drugs can make you feel strange or different. You must tell your parents and the study doctor if you feel sick when taking the study drugs.

- You may not be able to go to school or play or take part in activities for a little while.

- Other things may happen to you that we don't yet know about. You can say 'no' to what we ask you to do for the research at any time and we will stop.

5. Will I be paid to be in this study? You will not be paid for being in this study.

6. Do I have to be in the study? You and your family can choose to be part of this study or not. You and your family can also decide to stop being in this study at any time once you start. The doctors and nurses will still take care of you.There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional tumor tissue, bone marrow, and blood samples. We want to see if there are ways to tell how the cancer will respond to treatment. The tumor tissue and bone marrow samples will be taken at the same time as for your other procedures, so there would be no extra procedures. The blood samples will be taken at the same times that blood is collected for your other procedures so there will be no extra needle sticks. You can still take part in this study even if you don't allow us to collect extra tumor tissue, bone marrow, or blood samples for research.

APPENDIX G: PHARMACOKINETIC WORKSHEET FOR MAGROLIMAB, ARM A

COG Pt ID # _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg height _____cm.
Hu5F9-G4 (Magrolimab) Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion

Serum samples for PK analysis should be obtained according to instructions in Section 5.0

Record the exact date and time the sample is drawn

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	Priming (Safety Lead-In), Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Priming (Safety Lead-In), Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time: |__|__| : |__|__|**	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
2	Safety Lead-In, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Safety Lead-In, Day 8	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	**Dose on** Safety Lead-In, Day 1

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
3	Safety Lead-In, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Safety Lead-In, Day 15	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time: |__|__| : |__|__|**	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)

4	Cycle 1, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 1, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
5	Cycle 1, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 1, Day 8	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
6	Cycle 1, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 1, Day 15	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
7	Cycle 2, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 2, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
8	Cycle 3, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 3, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
9	Cycle 5, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 5, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
10	Cycle 7, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 7, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
11	Cycle 9, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 9, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
12	Cycle 11, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 11, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
13	End of Therapy	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Last dose given	**Date:**___/___/___	**Infusion Start Time:** |__|__| :	**Infusion Stop Time:** |__|__| : |__|__|	

		|__|__|	

One copy of this Pharmacokinetic Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 5.0, in addition to detailed guidelines for packaging and shipping samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples

APPENDIX H: PHARMACOKINETIC WORKSHEET FOR MAGROLIMAB, ARM B

COG Pt ID # _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg height _____cm.
Hu5F9-G4 (Magrolimab) Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion

Serum samples for PK analysis should be obtained according to instructions in Section 5.0.

Record the exact date and time the sample is drawn

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	Priming, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Priming, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| **:** |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
2	Cycle 1, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 1, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
3	Cycle 1, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 1, Day 8	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
4	Cycle 1, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 1, Day 15	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
5	Cycle 1, Day 22	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 1, Day 22	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
6	Cycle 2, Day 1	Prior to Hu5F9-G4 (magrolimab)/dinutuximab infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 2, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
7	Cycle 3, Day 1	Prior to Hu5F9-G4 (magrolimab)/dinutuximab infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 3, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
8	Cycle 5, Day 1	Prior to Hu5F9-G4 (magrolimab)/dinutuximab infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 5, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)

9	Cycle 7, Day 1	Prior to Hu5F9-G4 (magrolimab)/dinutuximab infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 7, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
10	Cycle 9, Day 1	Prior to Hu5F9-G4 (magrolimab)/dinutuximab infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 9, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
11	Cycle 11, Day 1	Prior to Hu5F9-G4 (magrolimab)/dinutuximab infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 11, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
12	Last dose given	Prior to Hu5F9-G4 (magrolimab)/dinutuximab infusion	___/___/___	|__|__| : |__|__|
Dose on Last dose given	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

One copy of this Pharmacokinetic Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 5.0, in addition to detailed guidelines for packaging and shipping samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples

APPENDIX I: ANTI-DRUG ANTIBODY (ADA) WORKSHEET FOR MAGROLIMAB

COG Pt ID # _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg
Hu5F9-G4 (Magrolimab) Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion

Serum samples will be collected in consenting patients in red top tubes at the timepoints listed in Section 5.0.

Record the exact date and time the sample is drawn.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	Priming, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Priming, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
2	Cycle 1, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 1, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
3	Cycle 2, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 2, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
4	Cycle 3, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 3, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

	__			
Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
5	Cycle 5, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 5, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
6	Cycle 7, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 7, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
7	Cycle 9, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 9, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
8	Cycle 11, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 11, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**

9	End of Therapy	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Last dose given	**Date:**___/___/__	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

The copy of this ADA Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 5.0, in addition to detailed guidelines for packaging and shipping samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples

APPENDIX J: FCR RECEPTOR POLYMORPHISM WORKSHEET FOR ARM A

COG Pt ID # _____

Please do not write patient names on this form or on samples.

Patient Weight: _____kg height _____cm.
Hu5F9-G4 (Magrolimab) Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion

PBMC samples for FcR receptor polymorphism analysis should be obtained according to instructions in Section 5.0.

Record the exact date and time the sample is drawn.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	Priming (Safety Lead-In), Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

The copy of this FcR Receptor Polymorphism Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 5.0, in addition to detailed guidelines for packaging and shipping samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples

APPENDIX K: FCR RECEPTOR POLYMORPHISM WORKSHEET FOR ARM B

COG Pt ID # _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg height _____cm.
Hu5F9-G4 (Magrolimab) Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion

PBMC samples for FcR receptor polymorphism analysis should be obtained according to instructions in Section 5.0.

Record the exact date and time the sample is drawn.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	Cycle 1, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

The copy of this FcR Receptor Polymorphism Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 5.0, in addition to detailed guidelines for packaging and shipping samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples

APPENDIX L: KIR PHENOTYPING WORKSHEET FOR ARM A

COG Pt ID # _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg height _____cm.
Hu5F9-G4 (Magrolimab) Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion

PBMC samples for KiR phenotyping should be obtained according to instructions in Section 5.0.

Record the exact date and time the sample is drawn):

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected
1	Priming (Safety Lead-In), day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

The copy of this KiR Phenotyping Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 5.0, in addition to detailed guidelines for packaging and shipping samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples

APPENDIX M: KIR PHENOTYPING WORKSHEET FOR ARM B

COG Pt ID # _____

Please do not write patient names on this form or on samples.

Patient Weight: _____kg height _____cm.

Hu5F9-G4 (Magrolimab) Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion

PBMC samples for KiR receptor polymorphism analysis should be obtained according to instructions in Section 5.0.

Record the exact date and time the sample is drawn.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected
1	Cycle 1, Day 1	Prior to Hu5F9-G4 (magrolimab)/dinutuximab infusion	___/___/___	|__|__| : |__|__|

The copy of this KiR Phenotyping Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 5.0, in addition to detailed guidelines for packaging and shipping samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____

(site personnel responsible for collection of samples

APPENDIX N: HUMAN ANTI-CHIMERA ANTIBODIES (HACA) TESTING WORKSHEET FOR ARM A

COG Pt ID # _____

Please do not write patient names on this form or on samples.

Patient Weight: _____kg

Hu5F9-G4 (Magrolimab) Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion

Dinutuximab Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion

Serum samples will be collected in red top tubes at the timepoints listed in Section 5.0.

Record the exact date and time the sample is drawn.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	Cycle 1, Day 1	Prior to dinutuximab infusion	___/___/___	|__|__| : |__|__|
2	Cycle 1, Day 5	Immediately after dinutuximab infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
3	Cycle 2, Day 1	Prior to dinutuximab infusion	___/___/___	|__|__| : |__|__|
4	Cycle 2, Day 5	Immediately after dinutuximab infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
5	Cycle 4, Day 1	Prior to dinutuximab infusion	___/___/___	|__|__| : |__|__|
6	Cycle 4, Day 5	Immediately after dinutuximab infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
7	End of Therapy		___/___/___	|__|__| : |__|__|

One copy of this HACA Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 5.0,, in addition to detailed guidelines for packaging and shipping samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____

(site personnel responsible for collection of samples)

APPENDIX O: HUMAN ANTI-CHIMERA ANTIBODIES (HACA) TESTING WORKSHEET FOR ARM B

COG Pt ID # _____

Please do not write patient names on this form or on samples.

Patient Weight: _____kg

Hu5F9-G4 (Magrolimab) Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion

Dinutuximab Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion

Serum samples will be collected in consenting patients in red top tubes at the timepoints listed in Section 5.0.

Record the exact date and time the sample is drawn.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	Cycle 1, Day 8	Prior to dinutuximab infusion	___/___/___	|__|__| : |__|__|
2	Cycle 1, Day 12	Immediately after dinutuximab infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
3	Cycle 2, Day 1	Prior to dinutuximab infusion	___/___/___	|__|__| : |__|__|
4	Cycle 2, Day 5	Immediately after dinutuximab infusion		

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
5	Cycle 4, Day 1	Prior to dinutuximab infusion	___/___/___	|__|__| : |__|__|
6	Cycle 4, Day 5	Immediately after dinutuximab infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
7	End of Therapy		___/___/___	|__|__| : |__|__|

One copy of this HACA Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 5.0, in addition to detailed guidelines for packaging and shipping samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____

(site personnel responsible for collection of samples)

APPENDIX P: LUMINEX FOR PERIPHERAL CYTOKINES WORKSHEET FOR ARM A

COG Pt ID # _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg height _____cm.
Hu5F9-G4 (Magrolimab) Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion
Dinutuximab Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion

Plasma will be collected according to instructions in Section 5.0.

Record the exact date and time the sample is drawn.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	Priming (Safety Lead-In), Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
2	Safety Lead-In, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
3	Safety Lead In, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Priming (Safety Lead-In), Week 1 Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
4	Cycle 1, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
5	Cycle 1, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
6	Cycle 1, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 1, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
7	Cycle 2, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

8	Cycle 2, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
9	Cycle 2, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 2, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
10	Cycle * 3, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 3, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
11	Cycle 4, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 4, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
12	Cycle 5, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 5, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
13	Cycle 6, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 6, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
14	Cycle 7, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 7, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
15	Cycle 8, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 8, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
16	Cycle 9, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 9, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
17	Cycle 10, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 10, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
18	Cycle 11, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Cycle 11, Day 1	___		

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
19	Cycle 12, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 12, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
20	End of Therapy		___/___/___	|__|__| : |__|__|
Dose on End of Therapy	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

*Fill out for as many cycles patient is on treatment

One copy of this Luminex for Peripheral Cytokines Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 5.0, in addition to detailed guidelines for packaging and shipping samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX Q: LUMINEX FOR PERIPHERAL CYTOKINES WORKSHEET FOR ARM B

COG Pt ID # _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg height _____cm.
Hu5F9-G4 (Magrolimab) Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion
Dinutuximab Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion

Plasma will be collected according to instructions in Section 5.0.

Record the exact date and time the sample is drawn.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	Priming, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Priming, Week 1 Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
2	Cycle 1, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
3	Cycle 1, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
4	Cycle 1, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 1, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
5	Cycle 2, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
6	Cycle 2, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
7	Cycle 2, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on	**Date:**___/___/	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Cycle 2, Day 1	___		

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
8	Cycle * 3, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 3, Day 1	**Date:** ___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
9	Cycle 4, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 4, Day 1	**Date:** ___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
10	Cycle 5, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 5, Day 1	**Date:** ___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
11	Cycle 6, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 6, Day 1	**Date:** ___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
12	Cycle 7, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Dose on Cycle 7, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
13	Cycle 8, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 8, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
14	Cycle 9, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 9, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
15	Cycle 10, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 10, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
16	Cycle 11, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 11, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**

17	Cycle 12, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
Dose on Cycle 12, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
18	End of Therapy		___/___/___	|__|__| : |__|__|
Dose on End of Therapy	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

*Fill out for as many cycles patient is on treatment

One copy of this Luminex for Peripheral Cytokines Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 5.0, in addition to detailed guidelines for packaging and shipping samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX R: CYTOF FOR PERIPHERAL IMMUNE SUBSETS WORKSHEET FOR ARM A

COG Pt ID # _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg height _____cm.
Hu5F9-G4 (Magrolimab) Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion
Dinutuximab Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion

Mononuclear cells from blood will be collected according to instructions in Section 5.0.

Record the exact date and time the sample is drawn.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	Priming (Safety Lead-In), Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
2	Safety Lead-In, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
3	Safety Lead In, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
4	Cycle 1, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
5	Cycle 1, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
6	Cycle 1, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
7	Cycle 2, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
8	Cycle 2, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
9	Cycle 2, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected

				(24-hr clock)
10	Cycle * 3, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
11	Cycle 4, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
12	Cycle 5, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
13	Cycle 6, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
14	Cycle 7, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
15	Cycle 8, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
16	Cycle 9, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample	Actual Time Sample

			Collected	Collected (24-hr clock)
17	Cycle 10, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
18	Cycle 11, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
19	Cycle 12, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
20	End of Therapy		___/___/___	|__|__| : |__|__|
Dose on End of Therapy	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|	

*Fill out for as many cycles patient is on treatment

One copy of this CyTOF Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 5.0, in addition to detailed guidelines for packaging and shipping samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX S: CYTOF FOR PERIPHERAL IMMUNE SUBSETS WORKSHEET FOR ARM B

COG Pt ID # _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg height _____cm.
Hu5F9-G4 (Magrolimab) Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion
Dinutuximab Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion

Mononuclear cells from blood will be collected according to instructions in Section 5.0.

Record the exact date and time the sample is drawn.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	Priming, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
2	Cycle 1, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
3	Cycle 1, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
4	Cycle 1, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
5	Cycle 2, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
6	Cycle 2, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
7	Cycle 2, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
8	Cycle * 3, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample	Actual Time Sample

			Collected	Collected (24-hr clock)
9	Cycle 4, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
10	Cycle 5, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
11	Cycle 6, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
12	Cycle 7, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
13	Cycle 8, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
14	Cycle 9, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
15	Cycle 10, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample	Time Point	Scheduled Collection Time	Actual Date	Actual Time

No.			Sample Collected	Sample Collected (24-hr clock)
16	Cycle 11, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
17	Cycle 12, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
18	End of Therapy		___/___/___	|__|__| : |__|__|

*Fill out for as many cycles patient is on treatment

One copy of this CyTOF Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 5.0, in addition to detailed guidelines for packaging and shipping samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX T: SAMPLE BANKING WORKSHEET FOR ARM A

COG Pt ID # _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg height _____cm.
Hu5F9-G4 (Magrolimab) Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion
Dinutuximab Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion

PBMC will be collected according to instructions in Section 5.0.

Record the exact date and time the sample is drawn.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	Priming, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
2	Safety Lead-In, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
3	Safety Lead In, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
4	Cycle 1, Day 1	Prior to Hu5F9-G4 (magrolimab)/dinutuximab infusion	___/___/___	|__|__| : |__|__|
5	Cycle 1, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
6	Cycle 1, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
7	Cycle 2, Day 1	Prior to Hu5F9-G4 (magrolimab)/dinutuximab infusion	___/___/___	|__|__| : |__|__|
8	Cycle 2, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
9	Cycle 2, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)

10	Cycle * 3, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
11	Cycle 4, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
12	Cycle 5, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
13	Cycle 6, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
14	Cycle 7, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
15	Cycle 8, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
16	Cycle 9, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected**

				(24-hr clock)
17	Cycle 10, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
18	Cycle 11, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
19	Cycle 12, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	**Time Point**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
20	End of Therapy		___/___/___	|__|__| : |__|__|

*Fill out for as many cycles patient is on treatment

One copy of this Sample Banking Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 5.0, in addition to detailed guidelines for packaging and shipping samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX U: SAMPLE BANKING WORKSHEET FOR ARM B

COG Pt ID # _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg height _____cm.
Hu5F9-G4 (Magrolimab) Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion
Dinutuximab Dose: _____ mg/kg Total Daily Dose: _____ mg IV infusion

PBMC will be collected according to instructions in Section 5.0.

Record the exact date and time the sample is drawn.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	Priming, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
2	Cycle 1, Day 1	Prior to Hu5F9-G4 (magrolimab)/dinutuximab infusion	___/___/___	|__|__| : |__|__|
3	Cycle 1, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
4	Cycle 1, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
5	Cycle 2, Day 1	Prior to Hu5F9-G4 (magrolimab)/dinutuximab infusion	___/___/___	|__|__| : |__|__|
6	Cycle 2, Day 8	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|
7	Cycle 2, Day 15	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
8	Cycle * 3, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample	Actual Time Sample

			Collected	Collected (24-hr clock)
9	Cycle 4, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
10	Cycle 5, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
11	Cycle 6, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
12	Cycle 7, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
13	Cycle 8, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
14	Cycle 9, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
15	Cycle 10, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample	Time Point	Scheduled Collection Time	Actual Date	Actual Time

No.			Sample Collected	Sample Collected (24-hr clock)
16	Cycle 11, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
17	Cycle 12, Day 1	Prior to Hu5F9-G4 (magrolimab) infusion	___/___/___	|__|__| : |__|__|

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
18	End of Therapy		___/___/___	|__|__| : |__|__|

*Fill out for as many cycles patient is on treatment

One copy of this Sample Banking Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 5.0, in addition to detailed guidelines for packaging and shipping samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX V: CENTRAL MONITORING PLAN

Central monitoring will be required for all patients enrolled at each site. All documents must be uploaded with 2 weeks of the corresponding time point or cycle.

Monitored Data	Protocol Section	CRF Question/ Data Element	Monitoring Conditionality	Source document	CTSU Document Type	Time point
Eligibility						
Confirmation of eligible diagnosis	3.1.1	*Pending final CRFs*	**Required**	E.g., Pathology report, CT report, MRI report, etc.	Pathology Report and Radiology Report	Enrollment
Performance Status	3.1.6	*Pending final CRFs*	**Required**	E.g., clinical note, eligibility checklist	Clinical Note or Eligibility Determination Checklist	
Adequate Bone Marrow function	3.1.7	*Pending final CRFs*	**Required**	Laboratory test report	Laboratory Report	
Adequate Organ function	3.1.7	*Pending final CRFs*	**Required**	Laboratory test report	Laboratory Report	
Adequate Cardiac Function	3.1.16	*Pending final CRFs*	**Required**	E.g., Echocardiogram, MUGA, Cardiac MRI	Echocardiogram or Scan Report(s)	
Informed Consent	3.1.15	*Pending final CRFs*	**Required**	Informed consent (redacted signature pages with dates)	Informed consent	
Drug Administration Elements						
Total **Hu5F9-G4 (magrolimab)** dose	6.0	*Pending final CRFs*	**Required**	Medication Administration Record (MAR)	Treatment Administration Document	Cycle 2 Cycle 4
Disease Evaluation Elements						
Tumor Disease Evaluation	12.0	*Pending final CRFs*	**Required**	E.g., CT report, MRI report, PET-CT report	Scan Report(s)	Cycle 2 Cycle 4

Labs/reports documenting protocol specific CTEP-AERS reportable events	10.0	*Pending final CRFs*	**Conditional:** If response is YES, CM is required	E.g., hospital admission report, laboratory reports, etc.	Relevant Document	Cycle 2 Cycle 4

Addressing Monitoring Findings
In the event that this monitoring identifies unacceptable procedures or significant deviations from protocol procedures, then the site will need to submit a corrective action plan to COGRegComp@childrensoncologygroup.org within two weeks.

In the event of significant repeated major deviations from the protocol, COGQA, in consultation with the study chair, may recommend that COG leadership suspend accrual at the site.