CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1b/2 Trial of Hu5F9-G4 in Combination with Cetuximab in Patients with Solid Tumors and Advanced Colorectal Cancer
Protocol Number:	5F9004
Investigational Medicinal Product:	Hu5F9-G4 in combination with cetuximab
Indication:	Solid tumors and colorectal cancer
Development Phase:	1b/2
US IND Number:	117687
Sponsor:	Forty Seven Inc. PPD Telephone: PPD Fax: PPD
Medical Monitor:	PPD PPD Telephone: PPD email: PPD
Study Monitor:	PPD PPD Telephone: PPD email: PPD
Lead Investigator:	PPD PPD PPD Telephone: PPD
Amendment 3 Date:	28 September 2018
Amendment 2 Date:	29 January 2017
Amendment 1 Date:	1 September 2016
Original Protocol Date:	29 July 2016

Compliance Statement:

This study will be conducted in accordance with Protocol 5F9004, the International Conference on Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and the applicable country and regional (local) regulatory requirements.

PROTOCOL APPROVAL PAGE

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

PPD

20 OCT 2018

Date

PPD

Forty Seven Inc.

PROTOCOL ACCEPTANCE PAGE

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

Investigator's Name: _____

Name of Institution/Site: _____

Signature: _____

Date: _____

SUMMARY OF CHANGES, AMENDMENT 3

The main reasons for amending the 5F9004 protocol are to modify the dose and schedule for Phase 1 cohorts, define the dose and schedule to be used in Phase 2, modify re-priming instructions, remove sample collection for receptor occupancy, allow for continuation of either drug in the combination as single-agent treatment, add assessment by iRECIST criteria, and to ensure consistency with other clinical studies of Hu5F9-G4 sponsored by Forty Seven Inc.

The following is a list of substantial changes that have been made to the protocol:

- Changed the Medical Monitor from PPD to PPD (Title page, Section 9.4).
- Changed the Study Monitor from PPD to PPD (Title page).
- Added the following terms and abbreviations definitions list: disease control rate, Enrolled Analysis Set, Per-Protocol Analysis Set, every 2 weeks, Response Evaluation Criteria in Solid Tumors, and Safety Analysis Set (Abbreviations and Definitions).
- Updated Hu5F9-G4 clinical safety data and clinical pharmacology data (Sections 1.2.4.1, 1.2.4.2, 1.5.1, and 6.1.5.2.1).
- Modified the planned Phase 1b doses administered in Cohort 4, which included the removal of the Hu5F9-G4 loading dose on Cycle 1 Day 11 and specification that the Hu5F9-G4 maintenance is 30 mg/kg or 45 mg/kg. Added that up to 5 dose cohorts are anticipated. (Synopsis, Study Design Schema, Sections 1.5.1, 3, and 6.1, 11.2, and Table 1 and Table 4).
- The Recommended Phase 2 dose and schedule (RP2DS) for Hu5F9-G4 was added. In Phase 2, patients will receive a priming dose of 1 mg/kg (i.e., no loading dose will be used), and maintenance doses of 30 mg/kg;

administration will be IV weekly during Cycle 1 and then every 2 weeks (Q2W) starting at Cycle 2 (cycle length is 28 days). Phase1b patients who have been on study for at least 8 weeks may be switched to the RP2DS, at the discretion of the Investigator. (Synopsis, Study Design Schema, Sections 1.5.1.2, 3.3, 3.4, 6.1, and Table 2 and Table 5). Based on emerging PK, pharmacodynamic and clinical data, the dosing regimen was changed to weekly dosing to improve patient convenience while maintaining potential efficacy and safety.

- The ability to explore multiple Phase 2 dose regimens in the Phase 2 portion of the protocol is being added to potentially evaluate alternative dosing regimens that may maximize potential efficacy and patient convenience. Additional safety run-in dohorts will not be required for other doses. (Synopsis, Sections 1.5.1.2, 3.1, 3.3, 3.4, 3.5, 6.1,and Table 2 and Table 5). An initial futility analysis after 15 evaluable patients for each dosing regimen is included to evaluate potential efficacy differences to enable further patient enrollment (Section 11.4).
- Modified the dose-limiting toxicity of Grade 3 infusion reaction to specify infusion reaction to Hu5F9-G4 or cetuximab (Section 3.2.4).
- Modified the re-priming instructions (new Section 6.1.3). Specified the timing and dose of Hu5F9-G4 required to obviate the effects of acute anemia that patients may experience after the first dose of drug. For patients undergoing repriming, safety-related laboratory tests and procedures are required.
- Modified the Dose Reductions and Delay Guidelines (Sections 6.1.3 and 6.1.4).
- Inclusion criterion 2b has been modified for subjects with KRAS wild-type CRC in Phase 2 in that patients must have only been refractory to (not relapsed from) prior anti- epidermal growth factor receptor (EGFR) therapy. Refractory is defined as failure to achieve an objective response, or progression during, any previous anti-EGFR containing regimen (monotherapy or in combination), or progression within 6 months of the last

dose. In addition, fluoropyrimidine was added to the criterion as a potential previous therapy (Synopsis, Section 4.1).

- Inclusion criterion 7 was modified to reduce the calculated glomerular filtration rate from >40 mL/min/1.73 m^2 to >30 mL/min/1.73 m^2) (Synopsis, Section 4.1).
- Exclusion criterion 12 was clarified to show that it is the IgG component of direct antiglobulin test (Synopsis, Section 4.2).
- Reduced the number of estimated sites from 14 to 8 (Section 3.8).

- Removal of sample collection for receptor occupancy studies in Phase 2 (Section 7.11, Table 5 and Table 6; deleted previous Table 10). At the current doses maximal RO appears to be achieved in the periphery; further collection in additional patients is unlikely to provide substantive scientific information or insights into dosing regimen, activity, or mechanism of action.

- Specified that patients could discontinue either drug in the combination and continue participation in the study while receiving single-agent treatment (either Hu5F9-G4 or cetuximab) (Sections 3 and 6). If the treating physician and Sponsor agree that it is in the best interest of the patient to continue treatment with either Hu5F9-G4 or cetuximab alone, the patient may continue to participate in the study provided that other protocol stipulations are met.

- Modified the secondary objectives and endpoints for Phase 1b and 2 to include disease control rate and time to progression (Synopsis, Sections 2.1.2, 2.2.2, and 11.3.1).

- Added the secondary objective and endpoint of objective response rate (ORR) as determined by use of iRECIST (Response Evaluation Criteria in Solid Tumors guidelines for use in trials testing immunotherapeutics) (Synopsis, Sections 2.1.2, 2.2.2, 6.1, 7.9, 10.1, 10.3 [new], and 11.3.1, and References). Incorporating iRECIST to address the potential for pseudoprogression and allowing for confirmation of tumor progression status.

- Added confirmed tumor progression according to iRECIST to the reasons for withdrawal from study treatments (Section 8.1). In order to address the potential for pseudoprogression and more accurately confirm disease progression as the reason for treatment discontinuation in cases where this is applicable.

- Specified that objective response rate (ORR) would be assessed in patients according to RECIST v 1.1 (primary endpoint) or iRECIST (secondary endpoint) (Synopsis, Sections 2.1.2, 2.2.2, 10.1, 10.3, and 11.3.1, and References). In order to address the potential for pseudoprogression and allow confirmation of tumor progression status.

- Correct an error in Table 10 (CD47 Receptor Occupancy Sample Time Points, Phase 1b [Table 9 in Amendment 2]). In the Cycle 1, Day 11, 72-hour time point, an errant footnote was shown; the footnote has been removed. Additionally, a new footnote (Footnote e) has been added that reads, “Sample to be collected from patients in non-loading dose cohort(s) only.”

- Added collection of archival tumor tissue biopsy samples from sites, including block or unstained slides.

Editorial changes and updates to style and formatting have been made to improve clarity and consistency throughout the document. Changes in sections of the protocol body have also been made in the protocol synopsis, study design schema, tabular schedules of assessments, and elsewhere in the document, as applicable.

PROTOCOL SYNOPSIS

Sponsor: Forty Seven Inc.

Investigational Agents: Hu5F9-G4 in combination with cetuximab

Protocol Number: 5F9004

Study Title: Protocol Number 5F9004: A Phase 1b/2 Trial of Hu5F9-G4 in Combination with Cetuximab in Patients with Solid Tumors and Advanced Colorectal Cancer

Scientific Rationale and Background

Metastatic colorectal cancer (CRC) is the second leading cause of cancer deaths in the United States (Siegel 2016). Although screening strategies have started to reduce the overall colorectal cancer death rate, the development of advanced metastatic disease is still associated with poor long-term survival. Systemic chemotherapy in combination with anti-epidermal growth factor receptor (EGFR) antibodies such as cetuximab and panitumumab have significantly improved prognosis in patients who have KRAS wild-type tumors (Lee 2015). However, patients with KRAS mutations, which comprise over 40% of colorectal cancers (Vaughn 2011), do not respond to anti-EGFR antibody therapies (Allegra 2009). Patients with KRAS mutant metastatic colorectal cancer have a poor prognosis with limited available therapies if they fail front line chemotherapy. The prognosis is also poor for patients with KRAS wild-type who progress during treatment and within 6 months after anti-EGFR monoclonal antibody treatment. Thus, additional therapies are needed to address this high unmet medical need in both patient populations.

Hu5F9-G4 is a humanized anti-human IgG4 monoclonal antibody (mAb) that binds to CD47 and blocks its interaction with its receptor, enabling phagocytosis of human cancer cells (Liu 2015b). The activity of Hu5F9-G4 is primarily dependent on blocking CD47 binding to SIRPα and not on the recruitment of Fc-dependent effector

functions, although the presence of the IgG4 Fc domain is required for its full activity. For this reason, Hu5F9-G4 was engineered with a human IgG4 isotype that is relatively inefficient at recruiting Fc-dependent effector functions that might enhance toxic effects on normal CD47 expressing cells (Liu 2015b). Preclinical studies using xenograft cancer models provide compelling evidence that Hu5F9-G4 triggers phagocytosis and elimination of cancer cells from human solid tumors and hematologic malignancies. Based on this mechanism of action (MOA) and its potent preclinical activity, Hu5F9-G4 is being developed as a novel therapeutic candidate for solid tumors and hematologic malignancies.

Metastatic colorectal cancer patients with both KRAS mutant and KRAS wild-type tumors who are refractory to treatment with standard treatment regimens have limited options for effective treatment. In patients with KRAS wild-type CRC who were refractory to all standard chemotherapy, cetuximab monotherapy significantly increases median survival over best supportive care from 4.8 months to 9.5 months (95% confidence interval [CI], 0.41 to 0.74; $P < 0.001$), but had no benefit for patients with KRAS mutated tumors (Karapetis 2008). However, even in patients with KRAS wild-type CRC, the objective response rate to single-agent cetuximab was only 12.8%; thus, there is still a substantial unmet medical need for these patients. Consequently, a monoclonal antibody targeting CD47 that enables phagocytosis and elimination of tumor cells and that demonstrates strong synergistic activity in combination with cetuximab in KRAS mutant and wild-type CRC would be an important therapeutic advance in the management of CRC patients.

To date, no significant overlapping toxicities between Hu5F9-G4 and cetuximab have been observed. The combination therapy of Hu5F9-G4 and cetuximab has shown strong preclinical evidence of activity in both RAS mutant and RAS wild-type CRC. This combination creates the potential to address an unmet medical need for these patients. The well-established tolerability of cetuximab and the manageable safety profile of Hu5F9-G4, together with the plans for rigorous safety monitoring in the Phase 1b part of this trial, suggests an acceptable risk-benefit profile for the advanced CRC patients enrolled in this study.

Study Objectives and Endpoints

The study objectives and endpoints are outlined in Synopsis Table 1.

Synopsis Table 1: Study Objectives and Endpoints

PRIMARY	
OBJECTIVES	**ENDPOINTS**
• To investigate the safety and tolerability, and to determine the recommended Phase 2 dose for Hu5F9-G4 in combination with cetuximab. • To evaluate overall response rate (ORR) of Hu5F9-G4 in combination with cetuximab in patients with KRAS mutant and KRAS wild-type CRC according to Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 (Eisenhauer 2009).	• Dose-limiting toxicities (DLTs) and adverse events (AEs) according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 4.03. • ORR using complete response (CR) + partial response (PR) as defined by the investigator according to RECIST v 1.1.
SECONDARY	
OBJECTIVES	**ENDPOINTS**
• To evaluate the pharmacokinetic (PK) profile of Hu5F9-G4 in combination with cetuximab. • To evaluate the immunogenicity of Hu5F9-G4 in combination with cetuximab. • To evaluate efficacy of Hu5F9-G4 in combination with cetuximab by the disease-control rate (DCR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and time to progression (TTP) for patients with KRAS mutant and KRAS wild-type CRC according to RECIST v 1.1 (Eisenhauer 2009). • To evaluate the ORR of Hu5F9-G4 in combination with cetuximab in patients with KRAS mutant and KRAS wild-type CRC according to iRECIST guidelines (Seymour 2017).	• Hu5F9-G4 concentration versus time measurements of Hu5F9-G4 in combination with cetuximab. • Anti-drug antibodies to Hu5F9-G4 and cetuximab. • DCR, DOR, PFS, OS, and TTP as defined by the Investigator according to RECIST v 1.1. • ORR using iCR + iPR as defined by the Investigator according to the iRECIST guidelines.
EXPLORATORY	
OBJECTIVES	**ENDPOINTS**
PPD	

Overall Study Design:

This trial is an open label, multicenter Phase 1b/2 trial investigating the combination of Hu5F9-G4 and cetuximab in patients with solid tumor and patients with advanced CRC. The study will be conducted in 2 parts:

- Dose escalation Phase 1b open to patients with solid tumors
- Phase 2 study with 2 treatment arms in patients with advanced/metastatic CRC whose tumors are either KRAS mutant or KRAS wild-type

The Phase 1b dose escalation part of the study will be conducted using a standard 3+3 dose escalation design to determine the maximum tolerated dose (MTD), if one exists, and to identify a recommended Phase 2 dose (RP2D) of Hu5F9-G4 in combination with cetuximab. Up to 5 dose level cohorts are anticipated.

The Phase 2 part of the study will then incorporate a safety run-in by treating 9 patients with KRAS wild-type tumors at the RP2D. If the tolerability of the regimen is confirmed in CRC patients, the study will begin to accrue patients with advanced CRC who have KRAS mutant tumors and continue to accrue patients who have KRAS wild-type tumors and who are relapsed or refractory to an anti-EGFR antibody therapy. Additional safety run-in cohorts will not be required if other doses are tested in Phase 2.

Phase 1b Study Design

In Cycle 1 of the Phase 1b part of the trial, the first dose escalation cohort will employ a Hu5F9-G4 priming dose of 1 mg/kg on Day 1 followed by 10-mg/kg maintenance doses on Days 8, 15, and 22. Cetuximab will be administered at a reduced dose of 300 mg/m^2 infused over 120-minutes on Day 8 followed by 200 mg/m^2 infusions given over 60 minutes on Days 15 and 22. During Weeks 2-4, Hu5F9-G4 and cetuximab will be administered on the same day. On all days on which both cetuximab and Hu5F9-G4 are given, cetuximab will be given first. Hu5F9-G4 will be given at least 1 hour after the cetuximab infusion is completed.

In Cycle 2, patients in the second dose escalation cohort will receive the same priming and maintenance dose regimen of Hu5F9-G4. If the starting dose of cetuximab in combination with Hu5F9-G4 is well tolerated the full standard dose of 400 mg/m^2 will be infused on Day 8 followed by 250 mg/m^2 infusions on Days 15 and 22. The dose of cetuximab used in the combination will not exceed the recommended single-agent dose and will be given during Cycle 3 and subsequent cycles. During Cycle 1, the weekly maintenance dose of Hu5F9-G4 will escalate to 20 mg/kg for patients in dose Cohort 3, assuming this dose level continues to be safe and well tolerated in the ongoing single-agent Phase 1 trial (Study SCI-CD47-001). Hu5F9-G4 will continue to be given weekly during subsequent cycles. Additional dose escalation of Hu5F9-G4 may continue in subsequent dose cohorts including the exploration of a loading dose in Week 2; however, the dose of Hu5F9-G4 may not exceed the single-agent MTD defined in ongoing studies. The anticipated dose levels are shown in Synopsis Table 2.

For the Phase 1b part of the study, the maintenance dose of Hu5F9-G4 for the first cohort will be 10 mg/kg. Dose escalation of the regimen will proceed through the designated dose levels, and decisions related to dose escalation will be based on the first 4 weeks of treatment in the current cohort, referred to as the "Dose-Limiting Toxicity (DLT) Assessment Period," in conjunction with ongoing assessments for patients in prior cohorts who continued therapy beyond 4 weeks. Decisions regarding additional cohorts to further refine the MTD or recommended Phase 2 dose and schedule (RP2DS) will be made by the Clinical Trial Steering Committee (CTSC). For example, the Hu5F9-G4 weekly maintenance dose schedule may be changed to every 2 or 3 weeks by the CTSC based on pharmacokinetic (PK) and clinical data review. In addition, adding intermediate dose steps (e.g., a maintenance dose cohort of 15 mg/kg weekly) or selecting a 10- or 20-mg/kg loading dose may be explored in new dose cohorts if supported by emerging PK and clinical data.

Synopsis Table 2: Phase 1b Dose Levels and Schedule

Dose Cohort	Drug/Dose (Intravenous)	Dose Schedule (Day per 28-day Cycle)	
		Cycle 1	Cycle 2+
1	Hu5F9-G4 1 mg/kg (prime) Hu5F9-G4 10 mg/kg (maintenance)	Day 1 Day 8, 15, 22	— Day 1, 8, 15, 22
	Cetuximab 300 mg/m^2 (load) Cetuximab 200 mg/m^2 (maintenance)	Day 8 Day 15, 22	 Day 1, 8, 15, 22
2	Hu5F9-G4 1 mg/kg (prime) Hu5F9-G4 10 mg/kg (maintenance)	Day 1 Day 8, 15, 22	— Day 1, 8, 15, 22
	Cetuximab 400 mg/m^2 (load) Cetuximab 250 mg/m^2 (maintenance)	Day 8 Day 15, 22	 Day 1, 8, 15, 22
3	Hu5F9-G4 1 mg/kg (prime) Hu5F9-G4 20 mg/kg (maintenance)	Day 1 Day 8, 15, 22	— Day 1, 8, 15, 22
	Cetuximab 400 mg/m^2 (load) Cetuximab 250 mg/m^2 (maintenance)	Day 8 Day 15, 22	 Day 1, 8, 15, 22
4 [a]	Hu5F9-G4 1 mg/kg (prime) Hu5F9-G4 30 mg/kg (maintenance) [b]	Day 1 Day 8, 15, 22	— Day 1, 8, 15, 22
	Cetuximab 400 mg/m^2 (load) Cetuximab 250 mg/m^2 (maintenance)	Day 8 Day 15, 22	— Day 1, 8, 15, 22
5	Hu5F9-G4 1 mg/kg (prime)	Day 1	—
	Hu5F9-G4 45 mg/kg (maintenance)	Day 8, 11,15, 22	Cycle 2: Day 1, 8, 15, 22 Cycle 3+: Day 1 and 15
	Cetuximab 400 mg/m^2 (load)	Day 8	—
	Cetuximab 250 mg/m^2 (maintenance)	Day 15, 22	Day 1, 8, 15, 22

a The Hu5F9-G4 loading dose was not administered in Cohort 4. Potential loading dose cohort may be added if deemed necessary by the Clinical Trial Steering Committee (CTSC).
b As recommended by CTSC, a 30-mg maintenance dose was administered in Cohort 4.

Phase 1b Dose Escalation

Dose escalation of Hu5F9-G4 and cetuximab in Phase 1b will follow a 3+3 study design. Three to 6 patients may be enrolled in each dose cohort. If none of the first 3 patients experiences a DLT, dose escalation will proceed to the next higher dose cohort. If 1 of the first 3 patients experiences a DLT, the cohort will be expanded to 6 patients. If more than 2 patients experience DLTs, the MTD dose level will have been exceeded, dose escalation will halt, and any additional patients will be treated at a lower dose level. The MTD for the Phase 1b is the highest dose level at which at least 6 patients are evaluable and less than 33% of these patients experience a DLT. The RP2D will be determined by the CTSC based on review of all available

safety, efficacy, PK, and pharmacodynamic data. The first patient in each dose cohort must complete at least 1 week of treatment before additional patients may be enrolled in the cohort. Subsequent patients may be enrolled simultaneously. The CTSC may expand the cohort by up to 6 additional patients for any dose level previously determined to be safe to collect additional safety and PK information and to confirm tolerability.

Dose-Limiting Toxicity Definition

Dose escalation decisions will be made by the CTSC based on the first 4 weeks of treatment for each patient, referred to as the "DLT Assessment Period." The last patient in a cohort must complete the DLT Assessment Period before new patients are escalated to a higher dose level.

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

- The patient experienced a DLT at any time after initiation of the first infusion of either Hu5F9-G4 or cetuximab.
- The patient completed at least 4 infusions of Hu5F9-G4 and 2 infusions of cetuximab.

Patients who withdraw before completing the 4-week DLT assessment period for reasons other than a DLT, or who do not fulfill either of the criteria above, will not be evaluable for assessment of DLT for dose review decisions and will be replaced in the cohort.

All toxicities will be graded according to the NCI CTCAE Version 4.03 (Appendix B), which provides additional guidance for AEs not specifically mentioned in CTCAE. A DLT is defined as any Grade 3 or greater AE that is assessed as related to study treatment that occurs during the 4-week DLT observation period. DLTs apply only to patients in the Phase 1b part of the study.

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

- Grade 3 anemia; however, Grade 3 hemolytic anemia that is medically significant, requiring hospitalization or prolongation of existing hospitalization, disabling, or limiting self-care activities of daily life (ADLs) is considered a DLT.
- Grade 3 indirect/unconjugated hyperbilirubinemia that resolves to ≤ Grade 2 with supportive care within 1 week and is not associated with other clinically significant consequences.
- Isolated Grade 3 electrolyte abnormalities that resolve to ≤ Grade 2 with supportive care within 1 week and are not associated with other clinically significant consequences.
- Grade 3 elevation in alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase that resolves to ≤ Grade 2 with supportive care within 1 week and is not associated with other clinically significant consequences.
- Grade 3 nausea, vomiting, or diarrhea that resolves to ≤ Grade 2 with supportive care within 72 hours
- Grade 3 fatigue that resolves to ≤ Grade 2 within 2 weeks on study.
- Grade 3 Hu5F9-G4 or cetuximab-related infusion reactions in the absence of an optimal pretreatment regimen, which is defined as acetaminophen or a comparable non-steroidal anti-inflammatory agent, plus an antihistamine and corticosteroids.
- Grade 3 tumor lysis syndrome or electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia) that resolve to ≤ Grade 2 or baseline within 1 week
- Grade 3 hypomagnesemia, that resolves to ≤ Grade 2 within 1 week
- Grade 3 or 4 lymphopenia or leukopenia

Phase 2 Study Design:

Once the Phase 1b dose escalation phase of the trial is completed and an RP2D determined, the CTSC will open the Phase 2 part of the study. Patients with

advanced CRC who have KRAS wild-type tumors will initially accrue until 9 patients are enrolled and have completed the DLT period. If the DLT rate in this CRC population does not exceed 33%, accrual will begin for patients who have KRAS mutant tumors and continue to accrue for patients who have KRAS wild-type tumors. Additional safety run-in cohorts will not be required if other doses are tested in Phase 2. Patients may be enrolled simultaneously without an observation time between patients. After the appropriate number of initial stage patients in each arm have been enrolled and followed for at least 8 weeks, an efficacy and safety analysis will be performed as described in the Statistical Analysis Plan (SAP). The CTSC will convene to review and approve proceeding with full accrual of either or both arms, or terminate either arm. Full accrual in either arm may be opened earlier by the CTSC at any point at which sufficient anti-cancer activity is observed. The CTSC may also approve further enrollment and exploration of additional alternate Phase 2 doses that may enhance efficacy.

Based on review of safety, efficacy, and PK data available from Phase 1b, the planned Phase 2 dose and schedule of Hu5F9-G4 that will be used in the Phase 2 part of this study and is shown in Synopsis Table 3.

When both study drugs are given on the same visit day, Hu5F9-G4 will be administered at least 1 hour after the completion of the cetuximab administration.

Starting with Cycle 2, the Day 8 and Day 22 dosing of Hu5F9-G4 has been removed (i.e., dosing is every 2 weeks [Q2W]). Patients enrolled in the Phase 1b part of the study who have been on study for at least 8 weeks may have their dose revised to the RP2DS, at the discretion of the Investigator.

Synopsis Table 3: Phase 2 Dose and Schedule

Drug/Dose (Intravenous)	Dose Schedule (Day per 28-day Cycle)		
	Cycle 1	**Cycle 2**	**Cycle 3+**
Hu5F9-G4 1 mg/kg (prime)	Day 1	—	—
Hu5F9-G4 30 mg/kg (maintenance)	Days 8, 15, and 22	Days 1 and 15	Days 1 and 15
Cetuximab 400 mg/m^2 (load)	Day 8	—	—
Cetuximab 250 mg/m^2 (maintenance)	Days 15 and 22	Days 1, 8, 15, and 22	Days 1, 8, 15, and 22
Hu5F9-G4 1 mg/kg (prime)	Day 1	—	—
Hu5F9-G4 45 mg/kg (maintenance) [a]	Days 8 ,11, 15, and 22	Days 1, 8, 15, and 22	Days 1 and 15
Cetuximab 400 mg/m^2 (load)	Day 8	—	—
Cetuximab 250 mg/m^2 (maintenance)	Days 15 and 22	Days 1, 8, 15, and 22	Days 1, 8, 15, and 22

- a If recommended by the Clinical Trial Steering Committee, other doses and schedules may be tested in Phase 2

Clinical Trial Steering Committee

The CTSC will oversee the conduct of the clinical trial. A representative from the Sponsor, usually the Study Medical Monitor or designee, will chair the CTSC.
The CTSC will have representation from each participating site in the study.
The CTSC will review safety and efficacy data generated during the trial and make decisions about patient recruitment, trial management, initiation of protocol specific amendments, expansion of cohorts, using higher or lower dose levels, defining any new dose cohorts, identification of the recommended dose for Phase 2 trials, including evaluation of multiple Phase 2 doses, and interim efficacy analysis decisions. The CTSC will meet at a minimum at the completion of each dosing cohort during dose escalation phase of the trial, at any protocol-specified formal interim analyses, and when emergent critical safety data are reported.
The composition, structure, and function of the CTSC are defined in the CTSC Charter.

Duration of Treatment

It is anticipated that this study will take approximately 42 months to complete.

Patient participation will include screening, treatment, and follow-up. Screening will last up to 30 days before first dose of study drugs, during which time the patient's eligibility and baseline characteristics will be determined. Treatment with study drugs may be continued until an unacceptable drug-related toxicity occurs, patient refusal, or until disease progression. Post treatment, patients will be observed for disease progression and survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

Overview of Assessments

Assessments will be performed according to the schedules provided in Protocol Section 7 (Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, and Table 10).

Planned Number of Patients

An estimated 15 to 24 patients will be enrolled in Phase 1b, depending on dose escalation and expansion.

Phase 2 includes 2 arms, one comprising patients with KRAS mutant CRC and the other comprising patients with KRAS wild-type CRC, in which enrollment in one or both arms may be modified based on emerging data. A total of 88 patients (44 patients per arm) will be enrolled in Phase 2, assuming progression to Stage 2 for both arms.

Inclusion Criteria

1. Adults ≥ 18 years old.
2. Histological Diagnosis
    a. Phase 1b only:
    Histologically or cytologically confirmed advanced solid malignancy with an emphasis on CRC, head and neck, breast, pancreatic and ovarian cancers who have been treated with at least one regimen of prior systemic

therapy, or who refuse systemic therapy, and for which there is no curative therapy available.

b. Phase 2:

- KRAS Mutant CRC: Histologically confirmed advanced KRAS mutant CRC who have progressed or are ineligible for fluoropyrimidine, irinotecan- and oxaliplatin-based chemotherapy

  OR

- KRAS Wild-Type CRC: Histologically confirmed advanced KRAS wild-type CRC who have progressed or are ineligible for fluoropyrimidine, irinotecan- and oxaliplatin-based chemotherapy and who are refractory to at least 1 prior systemic therapy that included an anti-EGFR antibody, such as cetuximab, panitumumab, or others. Patients should have disease progression during prior anti-EGFR therapy or within 6 months of the last day of treatment with the anti-EGFR

3. Eastern Cooperative Oncology Group (ECOG) Score 0-2.
4. For the Phase 2 part only: Disease that is measurable or assessable for response according to RECIST Version 1.1 Criteria.
5. Laboratory measurements, blood counts:
   - Hemoglobin ≥ 9.5 g/dL.
   - Absolute neutrophil count (ANC) ≥ 1.0×10^9/mL.
   - Platelets ≥ 75×10^9/ mL.
6. Laboratory measurements, hepatic function:
   - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) < 5× upper limit of normal (ULN).
   - Bilirubin < 1.5X ULN or 3.0× ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or a genetic equivalent.

7. Laboratory measurements, renal function:
   Serum creatinine ≤ 1.5×ULN or, if elevated, a calculated glomerular filtration rate (GFR > 30 mL/min/1.73 m^2).
8. Negative urine or serum pregnancy test within 30 days before administration of Hu5F9-G4 for women of childbearing potential.
9. Females of childbearing potential must be willing to use 1 effective method of contraception during the study and continue for 4 months after the last dose of Hu5F9-G4 and 6 months after the last dose of cetuximab.
10. Males must be willing to use 1 effective method of contraception and refrain from sperm donation during the study and continue for 4 months after the last dose of Hu5F9-G4 and 6 months after the last dose of cetuximab, if the partner is a female of childbearing potential.
11. Subject has provided informed consent.
12. Must be willing and able to comply with the clinic visits and procedures outlined in the study protocol.
13. Phase 2 only:
    Willing to consent to 1 mandatory pre-treatment and 1 on-treatment tumor biopsy, unless determined to not be feasible by the Investigator (reasons include, but are not limited to, lack of accessible tumor tissue to biopsy and patient safety issues).

Exclusion Criteria

1. Patients with active brain metastases (patients with stable treated central nervous system [CNS] lesions who are off corticosteroid and radiation therapy for at least 3 weeks are not considered active).
2. Prior anti-cancer therapy including chemotherapy, hormonal therapy, or investigational agents within 2 weeks or within at least 4 half-lives prior to Hu5F9-G4 dosing (up to a maximum of 4 weeks), whichever is longer. In all situations, the maximum required washout period will not exceed 4 weeks prior to the day of first treatment with Hu5F9-G4. Localized non-central nervous system (CNS) radiotherapy, previous hormonal therapy with luteinizing hormone releasing hormone (LHRH) agonists for prostate cancer,

low-dose steroids (oral prednisone or equivalent ≤ 20 mg per day), and treatment with bisphosphonates and RANKL inhibitors are not criteria for exclusion.

3. Prior treatment with CD47 or SIRPα-targeting agents.
4. Known active or chronic hepatitis B or C infection or human immunodeficiency virus (HIV).
5. Red blood cell (RBC) transfusion dependence, defined as requiring more than 2 units of RBC transfusions during the 4-week period prior to Screening. RBC transfusions are permitted during the Screening period and prior to enrollment to meet the hemoglobin inclusion criteria.
6. History of hemolytic anemia or Evans syndrome in the last 3 months.
7. Phase 2 only:
   Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancy for which treatment was completed at least 3 years ago and for which there is no evidence of recurrence.
8. Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients of cetuximab listed in Appendix A.
9. Significant medical diseases or conditions, as assessed by the Investigators and Sponsor, that would substantially increase the risk-benefit ratio of participating in the study. This includes, but is not limited to, acute myocardial infarction within the last 6 months, unstable angina, uncontrolled diabetes mellitus, significant active infections, severely immunocompromised state, and congestive heart failure New York Heart Association (NYHA) Class II-IV.
10. History of psychiatric illness or substance abuse likely to interfere with ability to comply with protocol requirements or give informed consent.
11. Pregnancy or active breast feeding.
12. Positive IgG component of the direct antiglobulin test (DAT).

Test Product, Dose, and Mode of Administration

Hu5F9-G4 is a humanized IgG4 monoclonal antibody that binds to human CD47 and blocks its interaction with its receptor, enabling phagocytosis of human cancer cells. Hu5F9-G4 drug product is provided in a liquid dosage form intended for intravenous (IV) infusion, supplied in single-use, 10-mL vials containing 200 mg of the antibody in a formulation of 10 mM sodium acetate, 5% (w/v) sorbitol, 0.01% (w/v) polysorbate 20, at pH of 5.0.

Erbitux® (cetuximab) is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human EGFR. Cetuximab is supplied at a concentration of 2 mg/mL as a 100 mg/50 mL, single-use vial or as a 200 mg/100 mL, single-use vial as a sterile, injectable liquid containing no preservatives. Cetuximab is formulated in a solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.41 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP.

Combination Therapy, Dose, and Mode of Administration

Study Endpoints

The study objectives and endpoints are outlined above in Synopsis Table 1.

Statistical Methods and Analyses

All analyses will be descriptive in nature. Descriptive statistics will be provided for all safety and efficacy endpoints.

All analyses will be conducted separately for patients in Phase 1b and Phase 2 parts of the study. However, safety analyses may be conducted for patients in both Phase 1b and Phase 2. In addition, efficacy analyses will be conducted separately for the two cohorts in Phase 2.

For continuous variables, the mean, standard deviation, median, and ranges will be provided. For categorical variables, the frequency and percentage in each category will be provided along with confidence intervals for primary and secondary efficacy

endpoints. For time-to-event variables, the Kaplan-Meier (KM) estimates and corresponding two-sided 95% confidence intervals for the median and quartiles will be provided. The KM plot may also be provided. Details regarding the statistical analysis to be conducted, including the handling of missing data and patient withdrawal, will be provided in the SAP.

Safety: The statistical analysis of safety will be conducted for patients in the safety analysis set (SAF). Safety variables to be examined include DLTs, treatment emergent adverse events (treatment-emergent adverse events [TEAEs]: AEs worsening or occurring during or after a patient's first exposure to study drugs), vital signs, physical examinations, laboratory, receptor occupancy, and antidrug antibody assessments. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 17.1 or later) and grouped by system organ class and preferred term.

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

Objective response is defined as CR+PR determined by RECIST v 1.1 (primary efficacy) and iCR+iPR determined by iRECIST (secondary efficacy) separately. ORR is defined as the proportion of patients with objective response in the Efficacy Analysis Set. A sensitivity analysis of ORR will be conducted on the Per Protocol Analysis Set if more than 10% of patients in the Efficacy Analysis Set are excluded from the Per Protocol Analysis Set.

Disease control is defined as CR + PR + stable disease (SD) determined by RECIST v 1.1. DCR is defined as the proportion of patients with disease control in the Efficacy Analysis Set.

DOR is measured from when the first (objective) response is met (i.e., CR or PR) until the first date of objectively documented progressive disease. Patients who do not have objectively progressive disease will be censored at their last documented progression-free date.

PFS is measured from dose initiation until the first date of objectively documented progression disease or death. Patients who do not have objectively documented progression disease AND not died will be censored at their last documented progression-free date.

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

TTP is measured from dose initiation until the first date of objectively documented progressive disease. Patients who do not have objectively documented progressive disease will be censored at their last documented progression-free date.

Pharmacokinetics: PK analysis will be conducted for Hu5F9-G4 and cetuximab using the PK Analysis Set (PAS). Based on the distinct MOAs of Hu5F9-G4 and cetuximab, drug-drug PK interactions are not expected. Thus, samples for PK analysis for cetuximab will be biobanked and will be analyzed based on CTSC recommendation. Summary statistics will be presented for Hu5F9-G4 serum concentrations at each scheduled time point. Descriptive graphical plots of individual serum concentration-versus-time profiles and mean concentration-versus-time profiles will be generated.

Dose Proportionality: The analysis of dose proportionality will be conducted for the area under the curve (AUC) and maximum concentration (C_{max}) of Hu5F9-G4 using a power model on log-transformed scale. The log-transformed PK parameters will each be regressed onto a fixed factor for log (dose). The 90% CI of the slope for each PK parameter will be computed from the model and presented in a summary table.

Immunogenicity Analyses: The rate and magnitude of anti-Hu5F9-G4 antibody positivity will be evaluated for individual patients, for all patients in the Phase 1b and 2 parts of the trial, and for the pooled patient population. PPD

PPD

Immunogenicity analysis will also be performed for cetuximab. However, it is not expected that Hu5F9-G4 will impact the immunogenicity of cetuximab and vice versa.

Pharmacodynamic and Biomarker Analyses: Several pharmacodynamic and correlative studies will be conducted on patient samples, as described in the SAP. PPD

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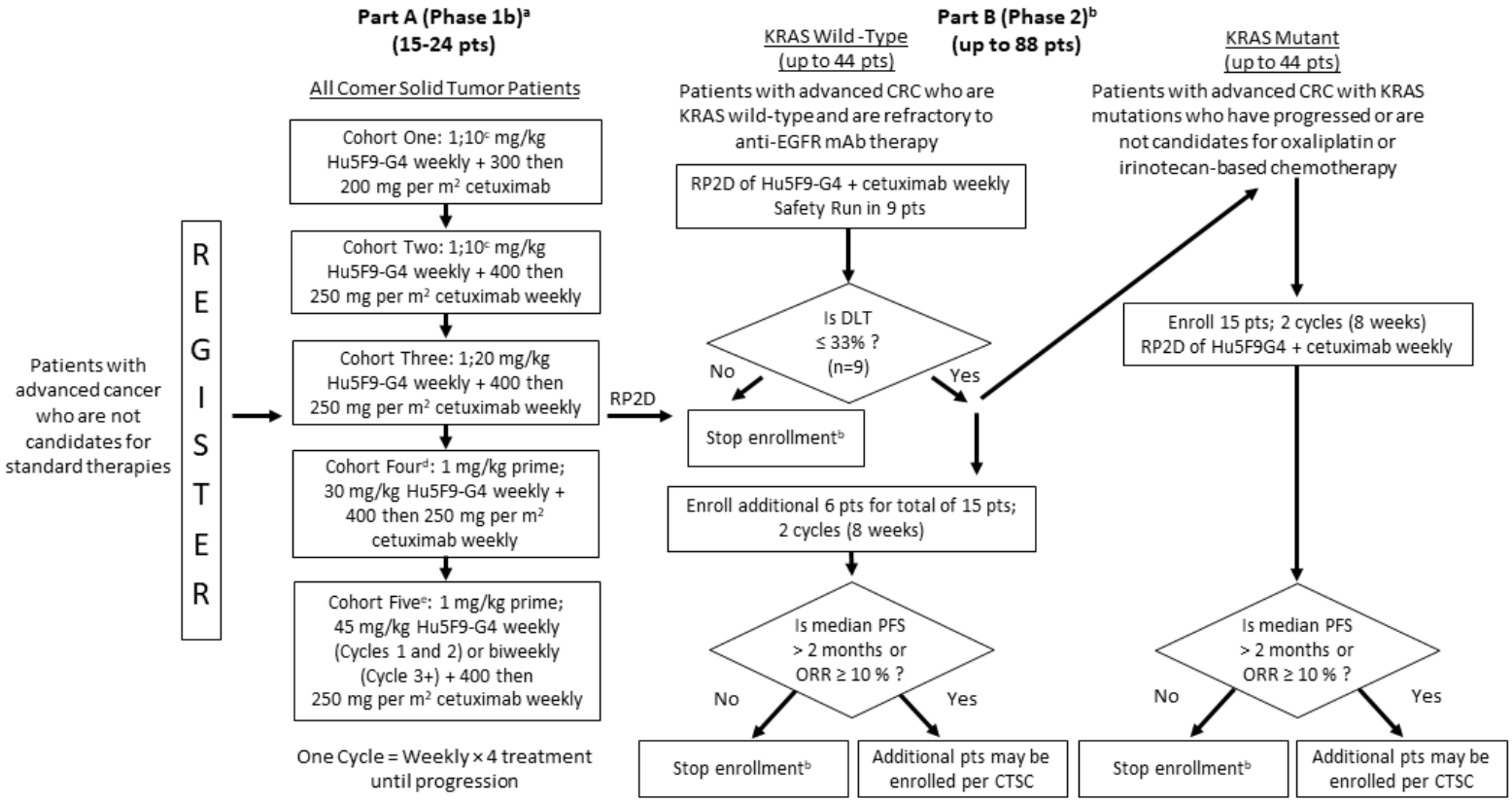
Sample Size Determination:

The total number of patients in this trial will include as many as 112 patients. This sample size includes the Phase 1b and Phase 2 parts of the study. In Phase 1b, a standard 3+3 dose escalation design will be used to explore the MTD of the investigational study drug combination in patients with solid tumors. An estimated 32 patients will be enrolled in Phase 1b, depending on dose escalation and expansion.

Phase 2 includes 2 arms, one comprising patients with KRAS mutant CRC and the other comprising patients with KRAS wild-type CRC, in which enrollment in one or both arms may be modified based on emerging data. A total of 88 patients (44 patients per arm) will be enrolled in Phase 2, assuming progression to Stage 2 for both arms. This sample size estimate was determined using a one-sided alpha level of 0.10 and a power of 0.80 based on a null hypothesis of 5% response rate compared to an alternative hypothesis of 15% for each cohort.

STUDY DESIGN SCHEMA

Study 5F9004 A Phase 1b/2 Trial of Hu5F9-G4 in Combination with Cetuximab in Solid Tumor and Advanced Colorectal Cancer Patients



Abbreviations: CRC = colorectal cancer; CTSC = Clinical Trial Steering Committee; EGFR = epidermal growth factor receptor; H0 = null hypothesis; H1 = alternative hypothesis; mAb = monoclonal antibody; ORR = objective response; PFS, progression-free survival; pts = patients.

[a] 3+3 dose escalation design.

[b] An alternative dose regimen may be evaluated in additional patients as determined by the CTSC. Once the initial safety run-in in 9 patients with KRAS wild-type cancer is completed and declared to be well-tolerated, a run-in phase with 9 patients with KRAS wild-type tumors will no longer be required if alternative Phase 2 dose regimens are going to be tested.

[c] 1,10 mg/kg represents a first priming dose of 1 mg/kg followed by a maintenance dose of 10 mg/kg of Hu5F9-G4 weekly thereafter, similarly for 1,20 mg/kg.

[d] Cohort Four Hu5F9-G4 dosing regimen will consist of 1 mg/kg priming dose on Day 1, followed by weekly maintenance doses of 30 mg/kg.

[e] Cohort Five Hu5F9-G4 dosing regimen will consist of 1 mg/kg priming dose on Day 1, followed by two 45 mg/kg doses in Cycle 1 Week 2 (Day 8 and loading dose Day 11), and then weekly maintenance doses of 45 mg/kg for the remainder of Cycle 1 and in Cycle 2, then biweekly (Days 1 and 15) maintenance doses for Cycle 3+.

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ABBREVIATIONS AND DEFINITIONS

ABO	any of the four blood groups A, B, AB, and O comprising the ABO system
ADA	antidrug antibodies
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BOR	best overall response
BUN	blood urea nitrogen
CBCs	complete blood counts
CFR	Code of Federal Regulations
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CRF	case report form (paper)
CRO	Clinical Research Organization
CT	computed tomography
CTSC	Clinical Trial Steering Committee
CyTOF	mass cytometry
DAT	direct antiglobulin test
DCR	disease-control rate
DLT	dose-limiting toxicity
DOR	duration of response
EAS	Efficacy Analysis Set
ECG	electrocardiogram
ECL	electrochemiluminescent
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

EDC	electronic data capture
EGFR	epidermal growth factor receptor
ENS	Enrolled Analysis Set
EOT	End of Treatment Visit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
H0	null hypothesis
H1	alternative hypothesis
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry
ILD	interstitial lung disease
INR	international normalized ratio
IR	immune response
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors guidelines for use in trials testing immunotherapeutics
IUD	intra-uterine device
IUS	intra-uterine hormone-releasing system
IV	intravenous
IWRS	interactive web response system
kg	kilogram
KM	Kaplan-Meier
L	liters
LDH	lactate dehydrogenase
LHRH	luteinizing-hormone releasing hormone
LISS	low ionic strength solution
LSC	leukemic stem cells
LTFU	long-term follow-up
M1	macrophages that suppress tumor progression
M2	macrophages that promote tumor progression
mAb	monoclonal antibody

MedDRA	Medical Dictionary of Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MOA	mechanism of action
MSI	microsatellite instability
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDC	National Drug Code
NHL	non-Hodgkin's lymphoma
NSG	NOD/SCID/IL2R gamma null
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PAS	Pharmacokinetic Analysis Set
PD	progressive disease
PeG	polyethylene glycol
PFS	progression-free survival
PPS	Per-Protocol Analysis Set
PK	pharmacokinetic(s)
PR	partial response
PRBC	packed red blood cell (transfusions)
PT	prothrombin time
Q2W	every 2 weeks
RBCs	red blood cells
REC	research ethics committee
RECIST	Response Evaluation Criteria in Solid Tumors
Rh	Rhesus factor
RO	receptor occupancy
RP2D	recommended Phase 2 dose
RP2DS	recommended Phase 2 dose and schedule
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	statistical analysis plan
SD	stable disease

SDV	source data verification
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIRPα	signal regulatory protein alpha
SOA	schedule of assessments
S-P	Ser-Pro
TEAE	treatment-emergent adverse event
TTP	time to tumor progression
ULN	upper limit of normal
WBCs	white blood cells

1. BACKGROUND

1.1. Colorectal Cancer

Metastatic colorectal cancer (CRC) is the second leading cause of cancer deaths in the United States (Siegel 2016). Although screening strategies have started to reduce the overall colorectal cancer death rate, the development of advanced metastatic disease is still associated with poor long-term survival. Systemic chemotherapy in combination with anti-epidermal growth factor receptor (EGFR) antibodies such as cetuximab and panitumumab have significantly improved prognosis in patients who have KRAS wild-type tumors (Lee 2015). However, patients with KRAS mutations, which comprise over 40% of colorectal cancers (Vaughn 2011), do not respond to anti-EGFR antibody therapies (Allegra 2009). Patients with KRAS mutant metastatic colorectal cancer have a poor prognosis with limited available therapies if they fail front line chemotherapy. The prognosis is also poor for patients with KRAS wild-type who progress during treatment and within 6 months after anti-EGFR monoclonal antibody treatment. Thus, additional therapies are needed to address this high unmet medical need in both patient populations.

1.2. Study Drug: Hu5F9-G4, a CD47-blocking Antibody

1.2.1. CD47 Biology

CD47 is a widely expressed cell surface protein that regulates of phagocytosis-mediated by cells of the innate immune system such as macrophages and dendritic cells. CD47 binds to and activates a receptor on innate immune cells, signal regulatory protein alpha (SIRPα), which initiates a signal transduction cascade that blocks phagocytosis. In this way, CD47 functions as a dominant inhibitor of phagocytosis by delivering a potent “don’t eat me” signal to phagocytic cells (Blazar 2001; Okazawa 2005). However, the complex process of phagocytosis depends on the relative balance of pro-phagocytic and anti-phagocytic inputs. Most normal cells, apart from aging red blood cells (Okazawa 2005; Oldenborg 2000), lack expression of corresponding pro-phagocytic signals (Chao 2012; Jaiswal 2009;

Majeti 2009), and, thus, are unaffected by CD47 blockade. In contrast, most cancer cells express pro-phagocytic signals on their cell surface, many of which are not yet molecularly characterized (Chao 2011b; Chao 2012). As a consequence, effective phagocytosis requires two distinct events: a silenced CD47/SIRPα pathway coupled with a pro-phagocytic signal.

CD47 is overexpressed in a broad range of human tumors, including colorectal cancer. The Weissman and Majeti laboratories originally identified increased CD47 expression on leukemic stem cells (LSC) in human acute myeloid leukemia (AML) (Chao 2010b; Majeti 2009). The increased expression of CD47 on cancer cells is presumed to prevent their phagocytic elimination by innate immune cells (Jaiswal 2009; Majeti 2009). These observations have since been extended to a diverse range of hematologic and solid tumor malignancies. Analysis of patient tumor and matched adjacent normal (non-tumor) tissue revealed that CD47 is overexpressed by approximately 3.3-fold in a panel of solid tumors including ovarian, breast, bladder, glioblastoma, hepatocellular carcinoma, prostate and colon cancer (Willingham 2012). CD47 mRNA expression levels correlated with a worse progression-free and overall survival for patients with ovarian, gliomas and glioblastomas (Willingham 2012).

CD47 appears to be an indispensable means by which cancer cells, including cancer stem cells, overcome intrinsic expression of their pro-phagocytic, “eat me,” signals (Chao 2010b; Chao 2012). When CD47 is blocked from interacting with SIRPα (e.g., using an antibody to CD47), these pro-phagocytic signals dominate, enabling phagocytosis of the cancer cells, which results in the inhibition of tumor growth and metastasis (Chao 2011b; Chao 2010a; Edris 2012a; Edris 2012b; Kim 2012; Majeti 2009; Willingham 2012; Liu 2015b). In addition to this direct anti-tumor effect, CD47 blockade also has the potential to induce an adaptive anti-tumor T-cell response through the cross-presentation of tumor antigens by macrophages and antigen-presenting cells following phagocytosis (Tseng 2013; Liu 2015a). Thus, the inhibition of CD47 signaling is a promising therapeutic strategy for targeting tumors using the innate and adaptive immune systems.

Most normal cells lack expression of pro-phagocytic signals and are unaffected by CD47 blockade. Red blood cells (RBCs) are a notable exception because CD47 expression protects RBCs from elimination by splenic red pulp macrophages, as well as sinusoidal macrophages, in liver and bone marrow. As RBCs age, they gradually lose CD47 expression and reorganize membrane phospholipids in a manner that enhances pro-phagocytic signaling, ultimately leading to their elimination by phagocytosis. The Weissman laboratory explored the effect of CD47 blockade on erythrocytes in primates by using monoclonal antibodies that bind to and inhibit CD47 signaling (Liu 2015b). Administration of CD47-blocking antibodies accelerates the phagocytotic process by substituting gradual loss of CD47 with immediate blockade of CD47 on aging RBCs, changing the balance between anti-phagocytic and pro-phagocytic signals in the RBC pool. In nonclinical studies, the premature loss of aging RBCs is compensated by an ensuing reticulocytosis, and the initial anemia resolves as aged RBCs are replaced with younger cells. Furthermore, in non-human primates, the risk of severe anemia is mitigated by the initial administration of a low, priming dose of anti-CD47 antibody that results in mild-to-moderate anemia and stimulates reticulocytosis.

1.2.2. Hu5F9-G4: A CD47-blocking Antibody

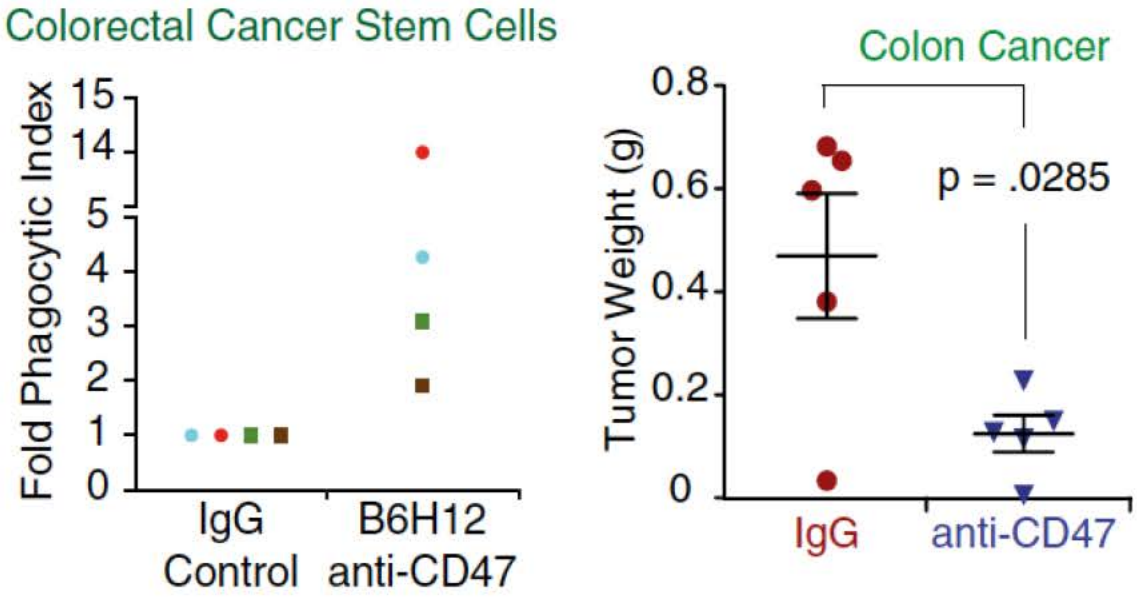
Hu5F9-G4 is a humanized anti-human IgG4 monoclonal antibody (mAb) that binds to CD47 and blocks its interaction with its receptor, enabling phagocytosis of human cancer cells (Liu 2015b). The activity of Hu5F9-G4 is primarily dependent on blocking CD47 binding to SIRPα and not on the recruitment of Fc-dependent effector functions, although the presence of the IgG4 Fc domain is required for its full activity. For this reason, Hu5F9-G4 was engineered with a human IgG4 isotype that is relatively inefficient at recruiting Fc-dependent effector functions that might enhance toxic effects on normal CD47 expressing cells (Liu 2015b). Preclinical studies using xenograft cancer models provide compelling evidence that Hu5F9-G4 triggers phagocytosis and elimination of cancer cells from human solid tumors and hematologic malignancies. Based on this mechanism of action (MOA) and its potent

preclinical activity, Hu5F9-G4 is being developed as a novel therapeutic candidate for solid tumors and hematologic malignancies.

1.2.3. Preclinical Studies

In preclinical models, anti-CD47 antibodies demonstrate anti-tumor activity against a broad range human solid tumors (breast, ovarian, colon, glioblastoma and others) (Willingham 2012; Edris 2012a) and hematologic malignancies (AML, acute lymphoblastic anemia [ALL], non-Hodgkin's lymphoma [NHL], myeloma, and others) (Majeti 2009; Chao 2011a; Chao 2010a; Chao 2011b; Kim 2012). In CRC laboratory models, anti-CD47 antibodies enhance the in vitro phagocytosis of CRC stem cells by macrophages and they also inhibit the in vivo growth of engrafted CRC tumor cells (Figure 1).

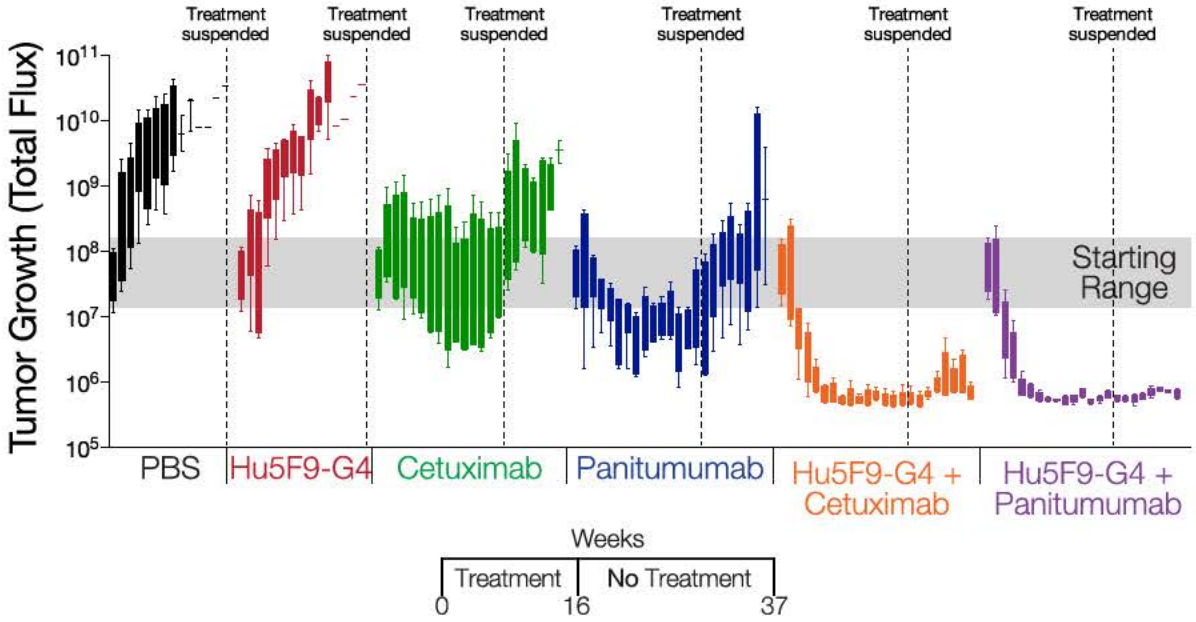
Figure 1. Preclinical Phagocytic and Anti-tumor Activity of Anti-CD47 Antibodies



Left Panel: Blockade of CD47–SIRPα interaction enables in vitro phagocytosis of patient-derived colorectal cancer stem cells by human peripheral blood-derived macrophages (squares) and NSG mouse bone marrow derived macrophages (circles). B6H12 is a murine anti-human CD47 monoclonal antibody that blocks CD47 binding to SIRPα. Right Panel: Anti-CD47 B6H12 antibody (500 µg daily IP) treatment inhibits the growth of engrafted human CRC tumors in an NSG mouse xenotransplantation model (Willingham 2012).

Anti-CD47 antibodies are also highly synergistic in combination with other anticancer therapies, including tumor-targeting monoclonal antibodies, such as cetuximab, panitumumab, rituximab, trastuzumab, and others (Chao 2010a; Chao 2011a; Willingham 2012; Liu 2015b; Forty Seven Inc., unpublished data). Tumor targeting antibodies with active Fc effector functions can provide strong pro-phagocytic signals that augment the anti-tumor effects of Hu5F9-G4. In preclinical studies in CRC, NOD/SCID/IL2R-gamma null (NSG) mice were subcutaneously implanted with UM8 colon cancer cells ($EGFR^+$) transduced with GFP-luciferase-encoding lentivirus. Twenty-eight days after engraftment, animals were treated with intraperitoneal injections of PBS control, cetuximab, panitumumab, Hu5F9-G4, or Hu5F9-G4 in combination with cetuximab or panitumumab (Figure 2; Study SU-RSR-16-002). Animals were treated every other day (PBS, Hu5F9-G4) or weekly (cetuximab, panitumumab) for 16 weeks. Treatment with Hu5F9-G4 alone in this model did not inhibit tumor growth, and treatment with cetuximab or panitumumab monotherapy stabilized tumor growth, but failed to produce a durable tumor remission. However, significant tumor regression and durable remissions were observed in all mice treated with Hu5F9-G4 in combination with cetuximab or panitumumab. Potent anti-tumor activity of Hu5F9-G4 in combination with cetuximab was also observed in both KRAS mutant and KRAS wild-type colorectal cancer models (Forty Seven Inc., unpublished data). No evidence of systemic toxicity such as body weight loss was observed in these combination studies, although Hu5F9-G4 does not cross-react with murine CD47. In summary, Hu5F9-G4 in combination with anti-EGFR antibodies such as cetuximab is a highly promising treatment for colorectal cancer, independent of RAS status.

Figure 2. Effect of Hu5F9-G4 in Combination with Cetuximab and Panitumumab in a Colon Cancer Xenograft Model



Source: Study SU-RSR-16-002

1.2.4. Hu5F9-G4 Clinical Studies

1.2.4.1. Summary of Hu5F9-G4 Clinical Safety

The safety of Hu5F9-G4 is currently being evaluated in two ongoing Phase 1 trials. The initial first-in-human Phase 1 trial (SCI-CD47-001) started dosing patients on 26 August 2014, and it is designed to determine the optimal dose and schedule of Hu5F9-G4 and to characterize its preliminary safety, pharmacokinetics (PK), and pharmacodynamics. This single institution study is enrolling patients with solid tumors and lymphomas; however, only solid tumor patients have been enrolled to date. A second Phase 1 trial (SCI-CD47-002) in relapsed refractory acute myeloid leukemia patients began dosing patients on 30 November 2015, and it is designed to define the maximum tolerated dose and to evaluate the safety, PK, and pharmacodynamics of Hu5F9-G4 in this patient population.

In 17 patients treated with Hu5F9-G4 (16 with solid tumors as of 4 February 2016, and 1 patient with AML as of 31 December 2015), Hu5F9-G4 has been well tolerated. The most common treatment-associated effects related to the

targeting of CD47 on erythrocytes, with anemia and RBC agglutination being most prominent. Other common treatment-related adverse events (AEs) include mild headache, fatigue, nausea, photopsia, urine discoloration, low back pain, and abdominal pain. Common drug-related abnormal laboratory findings include transient reticulocytosis, spherocytosis, hyperbilirubinemia, D-dimer elevation, and decreased haptoglobin. The majority of these findings occur following the first infusion, with very few study drug-related toxicities reported beyond the first cycle. In patients with solid tumors, the recommended priming dose of 1 mg/kg of Hu5F9-G4 was defined by the dose-limiting toxicities (DLTs) of acute abdominal pain and headache associated with hemagglutination. However, using a priming and maintenance dose schedule in these patients has allowed for the further escalation of the maintenance dose to 10-20 mg/kg.

As expected, the most common, clinically relevant toxicity is an acute anemia manifested as a 1- to 2-g/dL fall in hemoglobin observed during the first 1 to 2 weeks of treatment. In solid tumor patients, this is followed by a compensatory reticulocytosis and a gradual return to baseline by Week 3 or 4 despite continued dosing. These clinical observations are completely consistent with the known MOA of Hu5F9-G4 and the physiologic role of CD47 in regulating the turnover of aging erythrocytes. Other associated laboratory abnormalities including reticulocytosis, spherocytosis, transient hyperbilirubinemia (predominantly unconjugated), and decreased haptoglobin are all indicative of extravascular hemolysis consistent with phagocytic removal of RBCs due to blockade of CD47. No solid tumor patient has required a blood transfusion; however, the single patient enrolled to date in the AML Phase 1 study (SCI-CD47-002) was transfusion-dependent prior to study entry and has received frequent RBC transfusions without problems throughout the first 5 weeks on study.

A second treatment-related effect on erythrocytes is hemagglutination, which is presumed to result from the direct interaction of Hu5F9-G4 with CD47 on red blood cells. In Part A of the solid tumor Phase 1 study (SCI-CD47-001), hemagglutination was observed on peripheral blood smears in 8 out of 11 patients, typically within

24 hours of study drug administration. Although D-dimer elevation was also common, there was no evidence of disseminated intravascular coagulation, nor were there any signs of thrombocytopenia, coagulopathy, microangiopathy, thromboembolic disease, or other clinical sequelae associated with the hemagglutination findings. An asymptomatic solitary cotton wool spot was noted on retinal photographic examination in 1 solid tumor patient, but this was not associated with any hemagglutination and subsequently resolved.

1.2.4.2. Summary of Hu5F9-G4 Clinical Pharmacology

No formal clinical pharmacology trials have been completed with Hu5F9-G4; however, PK samples are being gathered from all patients in all ongoing studies after single and multiple doses. As of October 2017, approximately 1200 PK samples from 58 patients in the ongoing solid tumor Phase 1 study (SCI-CD47-001) had been analyzed using a validated enzyme-linked immunosorbent assay (ELISA). Samples are from Parts A, B, or C of the protocol. Hence, all patients were administered a single dose of 1 mg/kg (or less in Part A) on Day 1 of Week 1 followed by the target dose (1, 3, 10, 20, or 30 mg/kg once weekly, thereafter) from Day 8 onward. Patients in Part C received 2 doses of Hu5F9-G4 20 or 30 mg/kg in the week after priming dose followed by 20 or 30 mg/kg weekly afterwards. Overall, the data indicated nonlinearity in the PK profiles over the dose range 0.3–30 mg/kg; the terminal half-life was higher at the higher doses of 10–30 mg/kg compared to the lower doses indicating potential target-mediated drug disposition. Drug exposures were dose-proportional at doses ≥10 mg/kg and a typical antibody-like profile with extended half-life was seen at these doses.

The PK also showed time-variance between the first and second doses at the dose of 1 mg/kg. After the first dose of 1 mg/kg the maximum concentration (C_{max}) was approximately 0.7 mcg/mL, whereas that after the second dose of 1 mg/kg was approximately 10-fold higher. On subsequent dosing, there were no further changes in the PK at this dose level. Furthermore, at higher doses (3, 10, 20, and 30 mg/kg), the PK profile was roughly similar after the second and fifth doses, suggesting that

the time-variant PK only occurred at 1 mg/kg between the first and second weekly doses.

As of June 2017, in the solid tumor Phase 1 study, 2 of 41 patients (4.87%) treated tested positive for anti-drug antibodies (ADA) against Hu5F9-G4. In AML (Study SCI-CD47-002), 1 out of 13 patients (7.69%) had confirmed ADA samples, but the impact on drug PK could not be ascertained due to the limited amount of available PK data. The samples have not yet been tested for neutralizing antibodies. No unusual clinical toxicities have been observed in the patients with positive ADAs.

1.2.4.3. Summary of Hu5F9-G4 Clinical Efficacy

In the 2 ongoing Phase 1 clinical studies, dose escalation is continuing and efficacy data from patients with systemic Hu5F9-G4 exposures in the range associated with preclinical activity is still pending. No objective responses have been observed in 10 of the 13 patients with solid tumors who were evaluable for tumor response at the time of data cutoff in the ongoing dose escalation solid tumor Phase 1 study (SCI-CD47-001). Two patients with adenoid cystic carcinomas had stable disease for 33 and 72 weeks. In Study SCI-CD47-002, the single patient with AML treated thus far has had stable disease based on a Day 25 bone marrow evaluation and remains on study with stable disease after 5 weeks of treatment.

1.2.4.4. Summary of Hu5F9-G4 Clinical Experience

In summary, the expected adverse effects of anemia and hemagglutination have been observed in solid tumor and AML patients treated with Hu5F9-G4, but the overall safety profile to date is manageable and consistent with preclinical toxicology studies. All non-hematological Hu5F9-G4-associated toxicities have been transient and easy to manage. Supportive care with frequent RBC transfusions has been safely and successfully administered to an AML patient who was concurrently treated with Hu5F9-G4. Furthermore, implementation of a priming and maintenance dose strategy, coupled with the extension of the priming infusion duration to 3 hours, appear to substantially modulate the hematological toxicities of this novel agent,

thereby allowing dose escalation to continue in the ongoing Phase 1 studies. Nonclinical studies with Hu5F9-G4 in combination with anti-EGFR antibodies have been conducted in colorectal xenograft mouse models. No evidence of systemic toxicity, such as body weight loss, was observed in these combinations studies; however, Hu5F9-G4 does not cross-react with murine CD47 (Forty Seven Inc., unpublished data).

1.3. Cetuximab

Cetuximab (Erbitux®) is a commercially available chimeric mouse/human IgG1 kappa monoclonal antibody that targets EGFR (Appendix A). Its principal mechanism of action is through down regulation of the EGFR/KRAS/RAF/MAPK signaling pathway; although antibody-dependent cellular cytotoxicity may also be relevant (Fan 1993; Kurai 2007). It is approved for the treatment of KRAS wild-type CRC as a first-line agent and in later lines of therapy. It is not indicated for treatment of RAS-mutant colorectal cancers. Cetuximab is also approved for the treatment of squamous cell carcinoma of the head and neck in combination with radiation for locally advanced disease, or with platinum-based chemotherapy plus 5-fluorouracil for recurrent/metastatic disease. The most commonly observed adverse reactions associated with cetuximab treatment include cutaneous reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection. The most serious adverse reactions with cetuximab are infusion reactions, cardiopulmonary arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal failure, interstitial lung disease, and pulmonary embolus. Cetuximab exhibits non-linear PK with decreasing clearance observed at higher doses. After the administration of the recommended dose regimen of 400 mg/m^2 initial loading dose, followed by 250 mg/m^2 weekly doses, concentrations of cetuximab reached steady-state levels by the third weekly infusion. The mean half-life of cetuximab is approximately 112 hours (range 63–230 hours) (Appendix A).

1.4. Correlative Studies Background

Blockade of the CD47-SIRPα signaling axis on tumor cells by a monoclonal anti-CD47 antibody leads to tumor elimination by activation of both the innate and adaptive immune system. The anti-tumor activity of CD47 blocking antibodies is mediated by macrophages and other phagocytic cells of the innate immune system. Macrophages are a common immune cell infiltrate in many tumor types, with degree of intratumoral macrophage infiltrate correlating with clinical prognosis.
The correlation between macrophage infiltration and clinical disease course is often dependent on the presence of either classically activated (M1) type macrophages that suppress tumor progression or alternatively, activated (M2) type macrophages that promote tumor progression (Pollard 2004). Given the frequent infiltration of M2 macrophages in many tumor types and its role in promoting tumorigenesis, there is widespread interest in developing therapies that shift tumor macrophage polarization from the pro-tumorigenic M2 to the anti-tumorigenic M1 macrophages. In preclinical studies, anti-CD47 antibody-mediated tumor cell phagocytosis has been demonstrated to occur through both M1 and M2 macrophages (Zhang 2016). In addition, in vivo treatment of human xenograft tumors with anti-CD47 antibody demonstrated increased M1 intratumoral macrophages post-treatment (Zhang 2016), suggesting that anti-CD47 antibody can also shift the phenotype of macrophages from the M2 towards the M1 phenotype in vivo. Because the recruitment of macrophage effector cells is a key mechanism of anti-tumor activity for anti-CD47 antibodies, the characterization of macrophage tumor infiltration pre- and post-treatment may provide important insights into the degree of potential benefit seen in different patients and across various cancer subtypes.

In addition to modulating the innate immune system, anti-CD47 antibody therapy also activates the adaptive immune system towards an anti-tumor response. Phagocytosis of tumor cells by phagocytes (macrophages and/or dendritic cells) leads to cross-presentation of tumor antigens to T cells, enabling a T cell anti-tumor response (Tseng 2013; Liu 2015b). In one preclinical study, anti-CD47 antibody mediated a specific CD8 T cell anti-tumor response without proliferation of regulatory

T cells (which are generally thought to be tumor-promoting) (Tseng 2013). Currently, there is intense interest in investigating the relationship between T cell subsets that infiltrate the tumor and clinical response with the use of immune-oncology therapeutics. Indeed, increased T cell infiltration in the tumor has been associated with clinical response in oncology patients treated with T cell checkpoint inhibitors (Tumeh 2014; Herbst 2014). Given the role of anti-CD47 antibody in mediating an anti-tumor T cell response, the clinical investigation of the contribution of T cell effectors to anti-CD47 antibody-mediated efficacy is important to define how the innate and adaptive immune systems interact in various patients.

1.5. Starting Dose Rationale

1.5.1. Hu5F9-G4 Dose

1.5.1.1. Phase 1b Doses

In the Phase 1b part of the trial of Hu5F9-G4 in patients with solid tumors (SCI-CD47-001), the safety and PK of a 1-mg/kg priming dose followed by weekly maintenance doses of 10 ,20, 30, and 45 mg/kg weekly were to be explored (Forty Seven Inc., unpublished data). Pharmacokinetic modeling suggests that these dose levels should generate circulating Hu5F9-G4 drug concentrations that exceed those associated with anti-tumor efficacy in preclinical models. In the current Phase 1b trial, the first dose escalation cohort will receive 1 mg/kg of Hu5F9-G4 as a priming dose followed by weekly 10-mg/kg maintenance doses. This starting dose of up to 45 mg/kg weekly has been declared safe and well tolerated in the ongoing solid tumor single-agent Phase 1 trial. The dose of Hu5F9-G4 in combination with cetuximab will not exceed the maximum tolerated dose (MTD) for single-agent Hu5F9-G4 defined in the ongoing solid tumor Phase 1 trial (SCI-CD47-001).

1.5.1.2. Phase 2 Dose

The Clinical Trial Steering Committee (CTSC) has determined, based on the aggregate safety, efficacy, PK, and pharmacodynamic data obtained in the Phase 1b portion of this study (5F9004) that the dose of Hu5F9-G4 in the Phase 2

portion of this study will be as follows: A priming dose of 1 mg/kg and maintenance doses of 30 mg/kg; administration will be intravenous (IV) weekly during Cycle 1, and then every 2 weeks (Q2W) starting at Cycle 2 (cycle length is 28 days). Based on review of ongoing dosing data, the CTSC may recommend testing of multiple doses and schedules in Phase 2, including higher doses of Hu5F9.

1.5.2. Cetuximab Dose

Because the adverse effect profile of the combination of Hu5F9-G4 plus cetuximab is not known, a moderately reduced starting dose of cetuximab will be utilized in combination with Hu5F9-G4 to evaluate the initial safety of the combination regimen. Cetuximab will be started at a dose of 300 mg/m^2 initially followed by 200 mg/m^2 weekly in combination with Hu5F9-G4, which is a 25% and 20% reduction from the approved full cetuximab dose (400 mg/m^2 administered as a 120-minute intravenous infusion followed by 250 mg/m^2 weekly, infused over 60 minutes). If the starting dose in combination with Hu5F9-G4 is well tolerated, the dose of cetuximab will be escalated to the full recommended single-agent dose in the second dose cohort. The dose of Hu5F9-G4 will be escalated to the 20-mg/kg maintenance level only after the cetuximab dose is increased.

1.6. Study Rationale and Risk-Benefit

Metastatic colorectal cancer patients with both KRAS mutant and KRAS wild-type tumors who are refractory to standard treatment regimens have limited options for effective treatment. In patients with KRAS wild-type CRC who were refractory to all standard chemotherapy, cetuximab monotherapy significantly increases median survival over best supportive care from 4.8 months to 9.5 months (95% confidence interval, 0.41 to 0.74; P < 0.001), but had no benefit for patients with KRAS mutated tumors (Karapetis 2008). However, even in patients with KRAS wild-type CRC, the objective response rate to single-agent cetuximab was only 12.8%; thus, there is still a substantial unmet medical need for these patients. Consequently, a monoclonal antibody targeting CD47 that enables phagocytosis and elimination of tumor cells and that demonstrates strong synergistic activity in combination with cetuximab in

KRAS mutant and wild-type CRC would be an important therapeutic advance in the management of CRC patients.

To date, no significant overlapping toxicities between Hu5F9-G4 and cetuximab have been observed. Single-agent toxicity data are summarized in Section 1.2.4.1 for Hu5F9-G4 and in Section 1.3 for cetuximab. The safety risk of the proposed combination is not anticipated to be substantially increased beyond that associated with single-agent therapies. However, because the preclinical safety experience with this combination is limited, reduced starting doses of both Hu5F9-G4 and cetuximab will be utilized in the initial dose escalation Phase 1b part of this trial. The AE profile of this combination will be closely monitored using a standard 3+3 study design prior to further escalation.

The combination therapy of Hu5F9-G4 and cetuximab has shown strong preclinical evidence of activity in both RAS mutant and RAS wild-type CRC. This combination creates the potential to address an unmet medical need for these patients.
The well-established tolerability of cetuximab and the manageable safety profile of Hu5F9-G4, together with the plans for rigorous safety monitoring in the Phase 1b part of this trial, suggests an acceptable risk-benefit profile for the advanced CRC patients enrolled in this study.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

- To investigate the safety and tolerability, and to determine the recommended Phase 2 dose for Hu5F9-G4 in combination with cetuximab.
- To evaluate ORR of Hu5F9-G4 in combination with cetuximab in patients with KRAS mutant and KRAS wild-type CRC according to RECIST v 1.1 (Eisenhauer 2009).

2.1.2. Secondary Objectives

- To evaluate the PK profile of Hu5F9-G4 in combination with cetuximab.
- To evaluate the immunogenicity of Hu5F9-G4 in combination with cetuximab.
- To evaluate efficacy of Hu5F9-G4 in combination with cetuximab by the disease-control rate (DCR), DOR, PFS, OS, and TTP for patients with KRAS mutant and KRAS wild-type CRC according to RECIST v 1.1 (Eisenhauer 2009).
- To evaluate the ORR of Hu5F9-G4 in combination with cetuximab in patients with KRAS mutant and KRAS wild-type colorectal cancer (CRC) according to iRECIST guidelines (Seymour 2017).

2.1.3. Exploratory Objectives

PPD

2.2. Study Endpoints

2.2.1. Primary Endpoints

The primary endpoints for this study are:

- Dose-limiting toxicities (DLTs) in Phase 1b, and AEs according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

Version 4.03.

- ORR using CR + PR as defined by the investigator according to the RECIST Version 1.1 Criteria.

2.2.2. Secondary Endpoints

The secondary endpoints for this study are:

- Hu5F9-G4 concentration versus time measurements of Hu5F9-G4 in combination with cetuximab.
- Anti-drug antibodies to Hu5F9-G4 and cetuximab.
- DCR, DOR, PFS, OS, and TTP as defined by the Investigator according to the RECIST Version 1.1 Criteria.
- ORR using iCR + iPR as defined by the Investigator according to the iRECIST guidelines.

2.2.3. Exploratory Endpoints

3. STUDY DESIGN

3.1. Overall Study Design

This trial is an open label, multicenter Phase 1b/2 trial investigating the combination of Hu5F9-G4 and cetuximab in patients with solid tumor and patients with advanced CRC. The study will be conducted in 2 parts:

1. Dose escalation Phase 1b open to patients with solid tumors
2. Phase 2 study with 2 treatment arms in patients with advanced/metastatic CRC whose tumors are either KRAS mutant or KRAS wild-type

The Phase 1b dose escalation part of the study will be conducted using a standard 3+3 dose escalation design to determine the MTD, if one exists, and to identify a recommended Phase 2 dose (RP2D) of Hu5F9-G4 in combination with cetuximab. Up to 5 dose level cohorts are anticipated.

The Phase 2 part of the study will then incorporate a safety run-in by treating 9 patients with KRAS wild-type tumors at the RP2D. If the tolerability of the regimen is confirmed in CRC patients, the study will begin to accrue patients with advanced CRC who have KRAS mutant tumors and continue to accrue patients who have KRAS wild-type tumors and who are relapsed or refractory to an anti-EGFR antibody therapy. Additional safety run-in cohorts will not be required if other doses are tested in Phase 2. A total of up to 88 evaluable patients (44 patients with KRAS wild-type and 44 patients with KRAS mutant CRC) will be enrolled in the Phase 2 part. Patients who do not receive at least 2 doses of Hu5F9-G4 (of which at least 1 of the doses is a maintenance dose) may be replaced.

3.2. Phase 1b Study Design

3.2.1. Phase 1b Dose Levels

In Cycle 1 of the Phase 1b part of the trial, the first dose escalation cohort will employ a Hu5F9-G4 priming dose of 1 mg/kg on Day 1 followed by 10-mg/kg maintenance doses on Days 8, 15, and 22. Cetuximab will be administered at a reduced dose of 300 mg/m^2 infused over 120-minutes on Day 8 followed by

200 mg/m^2 infusions given over 60 minutes on Days 15 and 22. During Weeks 2-4, Hu5F9-G4 and cetuximab will be administered on the same day. On all days on which both cetuximab and Hu5F9-G4 are given, cetuximab will be given first. Hu5F9-G4 will be given at least 1 hour after the cetuximab infusion is completed.

In Cycle 2, patients in the second dose escalation cohort will receive the same priming and maintenance dose regimen of Hu5F9-G4. If the starting dose of cetuximab in combination with Hu5F9-G4 is well tolerated the full standard dose of 400 mg/m^2 will be infused on Day 8 followed by 250 mg/m^2 infusions on Days 15 and 22. The dose of cetuximab used in the combination will not exceed the recommended single-agent dose and will be given during Cycle 3 and subsequent cycles. During Cycle 1, the weekly maintenance dose of Hu5F9-G4 will escalate to 20 mg/kg for patients in dose Cohort 3, assuming this dose level continues to be safe and well tolerated in the ongoing single-agent Phase 1 trial (Study SCI-CD47-001). Hu5F9-G4 will continue to be given weekly during subsequent cycles. Additional dose escalation of Hu5F9-G4 may continue in subsequent dose cohorts including the exploration of a loading dose in Week 2; however, the dose of Hu5F9-G4 may not exceed the single-agent MTD defined in ongoing studies. The anticipated dose levels are shown in Table 1.

For the Phase 1b part of the study, the maintenance dose of Hu5F9-G4 for the first cohort will be 10 mg/kg. Dose escalation of the regimen will proceed through the designated dose levels, and decisions related to dose escalation will be based on the first 4 weeks of treatment in the current cohort, referred to as the “Dose-Limiting Toxicity (DLT) Assessment Period,” in conjunction with ongoing assessments for patients in prior cohorts who continued therapy beyond 4 weeks. Decisions regarding additional cohorts to further refine the MTD or recommended Phase 2 dose and schedule (RP2DS) will be made by the CTSC. For example, the Hu5F9-G4 weekly maintenance dose schedule may be changed to every 2 or 3 weeks by the CTSC based on PK and clinical data review. In addition, adding intermediate dose steps (e.g., a maintenance dose cohort of 15 mg/kg weekly) or

selecting a 10- or 20-mg/kg loading dose may be explored in new dose cohorts if supported by emerging PK and clinical data.

Table 1. Phase 1b Dose Levels and Schedule

Dose Cohort	Drug/Dose (Intravenous)	Dose Schedule (Day per 28-day Cycle)	
		Cycle 1	Cycle 2+
1	Hu5F9-G4 1 mg/kg (prime) Hu5F9-G4 10 mg/kg (maintenance)	Day 1 Day 8, 15, 22	— Day 1, 8, 15, 22
	Cetuximab 300 mg/m^2 (load) Cetuximab 200 mg/m^2 (maintenance)	Day 8 Day 15, 22	 Day 1, 8, 15, 22
2	Hu5F9-G4 1 mg/kg (prime) Hu5F9-G4 10 mg/kg (maintenance)	Day 1 Day 8, 15, 22	— Day 1, 8, 15, 22
	Cetuximab 400 mg/m^2 (load) Cetuximab 250 mg/m^2 (maintenance)	Day 8 Day 15, 22	 Day 1, 8, 15, 22
3	Hu5F9-G4 1 mg/kg (prime) Hu5F9-G4 20 mg/kg (maintenance)	Day 1 Day 8, 15, 22	— Day 1, 8, 15, 22
	Cetuximab 400 mg/m^2 (load) Cetuximab 250 mg/m^2 (maintenance)	Day 8 Day 15, 22	 Day 1, 8, 15, 22
4 [a]	Hu5F9-G4 1 mg/kg (prime) Hu5F9-G4 30 mg/kg (maintenance) [b]	Day 1 Day 8, 15, 22	— Day 1, 8, 15, 22
	Cetuximab 400 mg/m^2 (load) Cetuximab 250 mg/m^2 (maintenance)	Day 8 Day 15, 22	— Day 1, 8, 15, 22
5	Hu5F9-G4 1 mg/kg (prime)	Day 1	—
	Hu5F9-G4 45 mg/kg (maintenance)	Day 8, 15, 22	Cycle 2: Day 1, 8, 15, 22 Cycle 3+: Day 1 and 15
	Hu5F9-G4 45 mg/kg (loading)	Day 11	
	Cetuximab 400 mg/m^2 (load)	Day 8	—
	Cetuximab 250 mg/m^2 (maintenance)	Day 15, 22	Day 1, 8, 15, 22

a The Hu5F9-G4 loading dose was not administered in Cohort 4. Potential loading dose cohort may be added if deemed necessary by the Clinical Trial Steering Committee (CTSC).
b As recommended by CTSC, a 30-mg maintenance dose was administered in Cohort 4.

3.2.2. Phase 1b Dose Escalation

Dose escalation of Hu5F9-G4 and cetuximab in Phase 1b will follow a 3+3 study design. Three to 6 patients may be enrolled in each dose cohort. If none of the first 3 patients experiences a DLT, dose escalation will proceed to the next higher dose cohort. If 1 of the first 3 patients experiences a DLT, the cohort will be expanded to

6 patients. If more than 2 patients experience DLTs, the MTD dose level will have been exceeded, dose escalation will halt, and any additional patients will be treated at a lower dose level. The MTD for the Phase 1b is the highest dose level at which at least 6 patients are evaluable and less than 33% of these patients experience a DLT. The RP2D will be determined by the CTSC (Section 3.5) based on review of all available safety, efficacy, PK, and pharmacodynamic data. The first patient in each dose cohort must complete at least 1 week of treatment before additional patients may be enrolled in the cohort. Subsequent patients may be enrolled simultaneously. The CTSC may expand the cohort by up to 6 additional patients for any dose level previously determined to be safe to collect additional safety and PK information and to confirm tolerability.

3.2.3. Dose-limiting Toxicity Evaluation

Dose escalation decisions will be made by the CTSC based on the first 4 weeks of treatment for each patient, referred to as the "Dose-Limiting Toxicity (DLT) Assessment Period." The last patient in a cohort must complete the DLT Assessment Period before new patients are escalated to a higher dose level.

3.2.3.1. Definition of DLT-evaluable Patients

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

- The patient experienced a DLT at any time after initiation of the first infusion of either Hu5F9-G4 or cetuximab.
- The patient completed at least 4 infusions of Hu5F9-G4 and 2 infusions of cetuximab.

Patients who withdraw before completing the 4-week DLT assessment period for reasons other than a DLT, or who do not fulfill either of the criteria above, will not be evaluable for assessment of DLT for dose review decisions and will be replaced in the cohort.

3.2.4. Definition of Dose-limiting Toxicity

All toxicities will be graded according to the NCI CTCAE Version 4.03 (Appendix B). A DLT is defined as any Grade 3 or greater AE that is assessed as related to study treatment that occurs during the 4-week DLT observation period. DLTs apply only to patients in the Phase 1b part of the study.

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

- Grade 3 anemia; however, Grade 3 hemolytic anemia that is medically significant, requiring hospitalization or prolongation of existing hospitalization, disabling, or limiting self-care activities of daily life (ADLs) is considered a DLT.
- Grade 3 indirect/unconjugated hyperbilirubinemia that resolves to ≤ Grade 2 with supportive care within 1 week and is not associated with other clinically significant consequences.
- Isolated Grade 3 electrolyte abnormalities that resolve to ≤ Grade 2 with supportive care within 1 week and are not associated with other clinically significant consequences.
- Grade 3 elevation in alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase that resolves to ≤ Grade 2 with supportive care within 1 week and is not associated with other clinically significant consequences.
- Grade 3 nausea, vomiting, or diarrhea that resolves to ≤ Grade 2 with supportive care within 72 hours
- Grade 3 fatigue that resolves to ≤ Grade 2 within 2 weeks on study.
- Grade 3 Hu5F9-G4 or cetuximab-related infusion reactions in the absence of an optimal pretreatment regimen, which is defined as acetaminophen or a comparable non-steroidal anti-inflammatory agent, plus an antihistamine and corticosteroids.
- Grade 3 tumor lysis syndrome or electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia) that resolve to ≤ Grade 2 or baseline within 1 week
- Grade 3 hypomagnesemia, that resolves to ≤ Grade 2 within 1 week

- Grade 3 or 4 lymphopenia or leukopenia

3.3. Phase 2 Study Design

Once the Phase 1b dose escalation phase of the trial is completed and an RP2D determined, the CTSC will open the Phase 2 part of the study. Patients with advanced CRC who have KRAS wild-type tumors will initially accrue until 9 patients are enrolled and have completed the DLT period. If the DLT rate in this CRC population does not exceed 33%, accrual will begin for patients who have KRAS mutant tumors and continue to accrue for patients who have KRAS wild-type tumors. Patients may be enrolled simultaneously without an observation time between patients. Patients who do not receive at least 2 doses of Hu5F9-G4 (of which at least 1 of the doses is a maintenance dose) may be replaced. After the appropriate number of initial stage patients in each arm have been enrolled and followed for at least 8 weeks, an efficacy and safety analysis will be performed as described in the Statistical Analysis Plan (SAP). The CTSC will convene to review and approve proceeding with full accrual of either or both arms, or terminate either arm. Full accrual in either arm may be opened earlier by the CTSC at any point at which sufficient anti-cancer activity is observed. The CTSC may also approve further enrollment and exploration of additional alternate Phase 2 doses.

3.4. Planned Phase 2 Dose and Schedule

Based on review of safety, efficacy, and PK data available from Phase 1b, the planned and alternate Phase 2 dose and schedule of Hu5F9-G4 that will be used in the Phase 2 part of this study and is shown in Table 2.

When both study drugs are given on the same visit day, Hu5F9-G4 will be administered at least 1 hour after the completion of the cetuximab administration.

Starting with Cycle 2, the Day 8 and Day 22 dosing of Hu5F9-G4 has been removed, compared with the Phase 1b schedule (i.e., dosing is Q2W). Patients enrolled in the Phase 1b part of the study who have been on study for at least 8 weeks may have their dose revised to the RP2DS, at the discretion of the Investigator.

Table 2. Phase 2 Dose and Schedule

Drug/Dose (Intravenous)	Dose Schedule (Day per 28-day Cycle)		
	Cycle 1	**Cycle 2**	**Cycle 3+**
Current Dose and Schedule			
Hu5F9-G4 1 mg/kg (prime)	Day 1	—	—
Hu5F9-G4 30 mg/kg (maintenance)	Days 8, 15, and 22	Days 1 and 15	Days 1 and 15
Cetuximab 400 mg/m^2 (load)	Day 8	—	—
Cetuximab 250 mg/m^2 (maintenance)	Days 15 and 22	Days 1, 8, 15, and 22	Days 1, 8, 15, and 22
Alternate Dose and Schedule			
Hu5F9-G4 1 mg/kg (prime)	Day 1	—	—
Hu5F9-G4 45 mg/kg (maintenance) [a]	Days 8 ,11, 15, and 22	Days 1, 8, 15, and 22	Days 1 and 15
Cetuximab 400 mg/m^2 (load)	Day 8	—	—
Cetuximab 250 mg/m^2 (maintenance)	Days 15 and 22	Days 1, 8, 15, and 22	Days 1, 8, 15, and 22

a If recommended by the CTSC, other doses and schedules may be tested in Phase 2

3.5. Clinical Trial Steering Committee

The CTSC will oversee the conduct of the clinical trial. A representative from the Sponsor, usually the Study Medical Monitor or designee, will chair the CTSC.
The CTSC will have representation from each participating site in the study.
The CTSC will review safety and efficacy data generated during the trial and make decisions about patient recruitment, trial management, initiation of protocol specific amendments, expansion of cohorts, using higher or lower dose levels, defining any new dose cohorts, identification of the recommended dose for Phase 2 trials, including evaluation of multiple Phase 2 doses, and interim efficacy analysis decisions. The CTSC will meet at a minimum at the completion of each dosing cohort during dose escalation phase of the trial, at any protocol-specified formal interim analyses, and when emergent critical safety data are reported.
The composition, structure, and function of the CTSC are defined in the CTSC Charter.

3.6. Data Monitoring Committee

Data Monitoring Committee functions for this trial will be performed by the CTSC, as defined and described in Section 3.5.

3.7. Analysis of the Conduct of the Study

The CTSC, in conjunction with the Sponsor, will be the main body responsible for the analysis of the conduct of the study, as outlined in the CTSC charter.

3.8. Number of Sites

Approximately 8 sites located in the US will be included in this trial. Additional sites may be included based on enrollment and study timelines.

3.9. Estimated Study Duration

It is anticipated that this study will take approximately 42 months to complete.

Patient participation will include screening, treatment, and follow-up. Screening will last up to 30 days before first dose of study drugs, during which time the patient's eligibility and baseline characteristics will be determined. Treatment with study drugs may be continued until an unacceptable drug-related toxicity occurs, patient refusal, or until disease progression. Post treatment, patients will be observed for disease progression and survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

Recruitment will cease when one of the following occurs:

- Study treatment is considered too toxic to continue treatment before the anticipated number of patients are recruited. This assessment will be made by the CTSC.
- The stated number of patients to be recruited is reached. This number may be increased to include replacement patients for those who are not DLT evaluable or patients in Phase 2 who are not evaluable for efficacy as defined in Section 11; and patients added to intermediate dose or expanded cohorts as determined by the CTSC, and approved, if necessary, by the appropriate IRBs.

- The stated objectives of the trial are achieved.

Interim study database lock may be implemented at the discretion of the CTSC once all Phase 2 patients enrolled have achieved at least 1 tumor efficacy assessment.

4. SUBJECT SELECTION AND ENROLLMENT

4.1. Inclusion Criteria

1. Adults ≥ 18 years old.
2. Histological Diagnosis

    a. Phase 1b only:

    Histologically or cytologically confirmed advanced solid malignancy with an emphasis on CRC, head and neck, breast, pancreatic and ovarian cancers who have been treated with at least one regimen of prior systemic therapy, or who refuse systemic therapy, and for which there is no curative therapy available.

    b. Phase 2:

    - KRAS Mutant CRC: Histologically confirmed advanced KRAS mutant CRC who have progressed or are ineligible for fluoropyrimidine, irinotecan- and oxaliplatin-based chemotherapy

        OR

    - KRAS Wild-Type CRC: Histologically confirmed advanced KRAS wild-type CRC who have progressed or are ineligible for fluoropyrimidine, irinotecan- and oxaliplatin-based chemotherapy and who are refractory to at least 1 prior systemic therapy that included an anti-EGFR antibody, such as cetuximab, panitumumab, or others. Patients should have disease progression during prior anti-EGFR therapy or within 6 months of the last day of treatment with the anti-EGFR.

3. Eastern Cooperative Oncology Group (ECOG) Score 0-2.
4. For the Phase 2 part only: Disease that is measurable or assessable for response according to RECIST Version 1.1 Criteria.
5. Laboratory measurements, blood counts:
    - Hemoglobin ≥ 9.5 g/dL.
    - Absolute neutrophil count (ANC) ≥ 1.0×10^9/mL.

- Platelets ≥ 75 × 10^9/ mL.

6. Laboratory measurements, hepatic function:
   - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) < 5× upper limit of normal (ULN).
   - Bilirubin < 1.5X ULN or 3.0× ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or a genetic equivalent.

7. Laboratory measurements, renal function:
   Serum creatinine ≤ 1.5×ULN or, if elevated, a calculated glomerular filtration rate (GFR > 30 mL/min/1.73 m^2).
8. Negative urine or serum pregnancy test within 30 days before administration of Hu5F9-G4 for women of childbearing potential.
9. Females of childbearing potential must be willing to use 1 effective method of contraception during the study and continue for 4 months after the last dose of Hu5F9-G4 and 6 months after the last dose of cetuximab.
10. Males must be willing to use 1 effective method of contraception and refrain from sperm donation during the study and continue for 4 months after the last dose of Hu5F9-G4 and 6 months after the last dose of cetuximab, if the partner is a female of childbearing potential.
11. Subject has provided informed consent.
12. Must be willing and able to comply with the clinic visits and procedures outlined in the study protocol.
13. <u>Phase 2 only</u>:
    Willing to consent to 1 mandatory pre-treatment and 1 on-treatment tumor biopsy, unless determined to not be feasible by the Investigator (reasons include, but are not limited to, lack of accessible tumor tissue to biopsy and patient safety issues).

4.2. Exclusion Criteria

1. Patients with active brain metastases (patients with stable treated central nervous system [CNS] lesions who are off corticosteroid and radiation therapy for at least 3 weeks are not considered active).
2. Prior anti-cancer therapy including chemotherapy, hormonal therapy, or investigational agents within 2 weeks or within at least 4 half-lives prior to Hu5F9-G4 dosing (up to a maximum of 4 weeks), whichever is longer. In all situations, the maximum required washout period will not exceed 4 weeks prior to the day of first treatment with Hu5F9-G4. Localized non-CNS radiotherapy, previous hormonal therapy with luteinizing hormone releasing hormone (LHRH) agonists for prostate cancer, low-dose steroids (oral prednisone or equivalent ≤ 20 mg per day), and treatment with bisphosphonates and RANKL inhibitors are not criteria for exclusion.
3. Prior treatment with CD47 or SIRPα-targeting agents.
4. Known active or chronic hepatitis B or C infection or human immunodeficiency virus (HIV).
5. RBC transfusion dependence, defined as requiring more than 2 units of RBC transfusions during the 4-week period prior to Screening. RBC transfusions are permitted during the Screening period and prior to enrollment to meet the hemoglobin inclusion criteria.
6. History of hemolytic anemia or Evans syndrome in the last 3 months.
7. Phase 2 only:
   Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancy for which treatment was completed at least 3 years ago and for which there is no evidence of recurrence.
8. Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients of cetuximab listed in Appendix A.
9. Significant medical diseases or conditions, as assessed by the Investigators and Sponsor, that would substantially increase the risk-benefit ratio of participating in the study. This includes, but is not limited to, acute myocardial

infarction within the last 6 months, unstable angina, uncontrolled diabetes mellitus, significant active infections, severely immunocompromised state, and congestive heart failure New York Heart Association (NYHA) Class II-IV.

10. History of psychiatric illness or substance abuse likely to interfere with ability to comply with protocol requirements or give informed consent.
11. Pregnancy or active breast feeding.
12. Positive IgG component of the direct antiglobulin test (DAT).

4.3. Patient Screening

All patients who enter the Screening period for the study, which starts when the patient signs the informed consent form, receive a unique subject identification number before any study procedures are performed. This number is used to identify the patient throughout the clinical trial and must be used on all study documentation related to that patient, including if a patient is rescreened.

Patient Screening laboratory assessments may be tested repeatedly within the 30 days prior to the first dose of study treatment. Patients who screen fail may undergo repeated screening if the patient's medical condition has changed.

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

A patient is defined as enrolled in the study once all eligibility criteria have been satisfied and the Sponsor or designee has confirmed the cohort or study arm assignment. After signing the informed consent, eligible patients are expected to receive the first dose of Hu5F9-G4 (Study Day 1) within 30 days.

4.4. Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the Institutional Review Board/Research Ethics Committee (IRB/REC) approved informed consent form (ICF) prior to participation in any study specific procedure. Data from assessments performed as part of standard

of care prior to ICF signature may be used if they are within the required Screening period. The participant must receive a copy of the signed and dated consent documents. A signed copy (in paper or electronic format) of the consent documents must be retained in the medical record or research file.

4.5. Registration Process

Patient will be assigned the subject number at the time of consent. The site will register the patient through interactive web response technology (IWRS) with the Sponsor or representative within 2 days of consent.

Prior to being assigned a dose cohort or treatment arm, patients must have signed the informed consent and satisfied all of the eligibility criteria. Once patients have been assigned to a dose cohort or treatment arm, they will be considered enrolled. The Investigator will determine the eligibility of the patient.

5. STUDY DRUG INFORMATION

See the Pharmacy Manual for detailed instructions for Hu5F9-G4 and cetuximab preparation and handling.

5.1. Hu5F9-G4

5.1.1. Physical Description of Study Drug

The active pharmaceutical ingredient (API) is Hu5F9-G4, a humanized IgG4 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 Fab arm exchange. It comprises a disulfide-linked glycosylated tetramer, consisting of two identical 444 amino acid heavy gamma chains and two identical 219 amino acid kappa light chains. Hu5F9-G4 targets the human CD47 antigen. Hu5F9-G4 drug product is a sterile, clear, colorless, preservative-free liquid intended for intravenous (IV) infusion.

Hu5F9-G4 active pharmaceutical ingredient (API) is manufactured under current Good Manufacturing Practices.

Hu5F9-G4 is supplied in single-use, 10-mL vials containing 200 mg of the antibody in a formulation of 10 mM sodium acetate, 5% (w/v) sorbitol, 0.01% (w/v) polysorbate 20, at pH of 5.0.

The labeling complies with the requirements of the applicable regulatory agencies.

Additional details about Hu5F9-G4 are provided in the Pharmacy Manual.

5.2. Cetuximab

5.2.1. Physical Description of Study Drug

Erbitux® (cetuximab) is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). Cetuximab is composed of the Fv regions of a mouse anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions

and has an approximate molecular weight of 152 kDa. Cetuximab is produced in mammalian (murine myeloma) cell culture.

Cetuximab is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous cetuximab particulates. Cetuximab is supplied at a concentration of 2 mg/mL as a 100 mg/50 mL single-use vial (NDC 66733 948 23), or as a 200 mg/100 mL single-use vial (NDC 66733 958 23) as a sterile, injectable liquid containing no preservatives individually packaged in a carton. Cetuximab is formulated in a solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.41 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP (Appendix A).

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) and do not freeze. Increased particulate formation may occur at temperatures at or below 0°C. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2°C to 8°C (36°F to 46°F) and up to 8 hours at controlled room temperature (20°C to 25°C; 68°F to 77°F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2°C to 8°C. Discard any unused portion of the vial.

6. TREATMENT PLAN

6.1. Study Drug Administration Guidance: Hu5F9-G4 and Cetuximab

6.1.1. Dosing

Planned Phase 1b dose levels are presented in Table 1 and the Phase 2 dose and schedule is presented in Table 2.

The dose of each study drug will be calculated based on actual weight at enrollment (using weight obtained either at Screening or on Day 1) and remains constant throughout the study, unless there is a > 10% change in weight from baseline. Modifications to the study drug doses administered should be made for a > 10% change in body weight and for dose modifications as described in Section 6.1.4. Dose modifications for changes in body weight < 10% may be made according to local institutional guidelines.

All patients will receive an Hu5F9-G4 priming dose of 1 mg/kg on Day 1.
The duration of the infusion of the priming dose will be 3 hours (± 30 minutes).
The priming dose will be followed by a weekly maintenance dose. The duration of the infusion of the maintenance dose will be 2 hours (± 30 minutes). The first maintenance dose will be administered starting on Day 8 after the completion of the first dose of cetuximab. All subsequent maintenance doses of Hu5F9-G4 will be administered at the start of each study week (± 1 day). Hu5F9-G4 will be administered at least 1 hour after the completion of cetuximab administration.

All patients should be monitored for at least 1 hour post-infusion for the first 4 weeks.
Post-infusion monitoring should begin after the last study drug is given.
Post-infusion monitoring is not required for doses after Cycle 1. Patients who experience any treatment-related AEs during the observation period should be further monitored, as clinically appropriate.

Patients will receive a cetuximab dose of 300-400 mg/m^2 given IV starting on Day 8, followed by weekly dosing at 200-250 mg/m^2 on Days 15 and 22. Starting at

Cycle 2, and for each cycle thereafter, cetuximab will be given weekly starting on Day 1. (Details are provided in Section 6.1.4.2.)

Because of the possibility of an initial increase in tumor burden caused by immune cell infiltration in the setting of a T-cell response (termed pseudoprogression) with immunotherapy treatment, radiographic progression defined as unconfirmed progressive disease according to iRECIST (Seymour 2017) may not be indicative of true PD. Hu5F9-G4 and cetuximab combination treatment may continue past the initial determination of disease progression according to iRECIST as long as the following criteria are met:

- No new symptoms or worsening of previous symptoms
- Tolerance of Hu5F9-G4 and avelumab
- Stable ECOG performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (for example, central nervous system [CNS] metastases)

6.1.2. Premedication

Premedication is required before administration of the first cetuximab dose and before the first 2 doses of Hu5F9-G4 (inclusive of the priming dose). At the discretion of the Investigator, administration of premedication may continue for subsequent doses of cetuximab and/or Hu5F9-G4.

Hu5F9-G4

Premedication with oral acetaminophen 650 to 1000 mg and oral or intravenous diphenhydramine 25 mg, or comparable regimen, is required before administration of the first 2 doses of Hu5F9-G4 (inclusive of the priming dose. Premedication may be given at any time on the day(s) of dosing, up to 15 minutes prior to dosing. Premedication for subsequent Hu5F9-G4 treatments may be continued based upon the treating physician's clinical judgement and the presence/severity of prior

infusion-related reactions. Premedications used to manage infusion-related reactions are described in Sections 6.1.4.2.2 and 6.1.5.2.4.

Cetuximab

From 30 to 60 minutes prior to administration of the first dose of cetuximab, patients should be premedicated with an H1 antagonist (e.g., 50 mg of diphenhydramine) intravenously. Continued use of premedications plus the addition of other agents (i.e., glucocorticoids, etc.) should be implemented as required by local standards of practice and at the discretion of the Investigator.

6.1.3. Repriming

The following list describes the requirements for Hu5F9-G4 repriming.

- Patients who experience an interruption of >2 weeks after receiving only the priming dose (1 mg/kg) must be "reprimed" by receiving the Hu5F9-G4 priming dose of 1 mg/kg IV over 3 hours (±30 minutes) and 3 subsequent weekly maintenance doses prior to starting the Q2W dosing schedule.
- Patients who experience an interruption of >4 weeks after receiving at least 1 maintenance dose (i.e., 30 mg/kg) must be "reprimed" by receiving the Hu5F9-G4 priming dose of 1 mg/kg IV over 3 hours (±30 minutes) and 3 weekly maintenance doses prior to starting the Q2W schedule.
- Cetuximab must be administered as regularly scheduled (e.g. Hu5F9-G4 repriming doses may be administered on the same day as cetuximab is given and administration of cetuximab once weekly should be maintained.)
- Premedication is required for the repriming dose and the first weekly maintenance dose (Section 6.1.2).

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

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

- Complete blood count (CBC) with differential, platelets, reticulocytes

- Peripheral blood smear
- Serum chemistry
- Haptoglobin, D-dimer, thrombin, fibrinogen
- PT/INR, aPTT
- Vital signs
- Physical examination
- Adverse events
- Concomitant medications

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

6.1.4.1. Hu5F9-G4

Dose modification or dose delay of Hu5F9-G4 may not occur for patients in the initial 28-day DLT assessment period in the Phase 1b part of the study or for patients in the first cycle of the Phase 2 part of the study. After the initial 28-day treatment period for evaluation of DLTs, Hu5F9-G4 may be withheld if treatment-emergent Hu5F9-G4-related AEs occur, which include all AEs that constitute a DLT as defined in Section 3.2.4. If the severity has recovered to Grade 0 to 2 within 4 weeks and in the absence of disease progression, Hu5F9-G4 may be re-introduced at the next lower dose level. Patients who experience a DLT of either hemolytic anemia or Grade ≥ 4 non-hematological toxicity will not restart Hu5F9-G4 and will be withdrawn from study drug treatment. Restarting treatment after a delay of more than 4 weeks (such as for an unrelated medical condition with expected recovery) must be approved by the medical monitor.

Patients with an interruption or treatment delay of longer than 2 weeks after receiving only the priming dose (1 mg/kg) or >4 weeks after receiving at least 1 maintenance dose (e.g., 30 mg/kg) must be “reprimed” by receiving the priming dose of 1 mg/kg IV over 3 hours (±30 minutes) and 3 subsequent weekly maintenance doses following the repriming dose prior to resuming the Q2W dosing schedule (Section 6.1.3, Repriming).

6.1.4.1.1. Interruption of Hu5F9-G4 Treatment

For patients who experience dose interruptions, instructions for repriming are provided in Section 6.1.3.

6.1.4.1.2. Maintenance Dose Schedule Modification

Patients who have completed at least 8 weeks of weekly maintenance therapy may stay at the same infusion dose, but may have their Hu5F9-G4 schedule of administration extended to every 2 or 3 weeks, if supported by PK data and approved by the CTSC.

6.1.4.1.3. Intra-patient Dose Escalation

In the Phase 1b part of the study, patients who have been on study for at least 8 weeks may have their maintenance dose escalated to a higher dose level that has been previously demonstrated to be safe in this study, at the discretion of the Investigator and the CTSC.

6.1.4.2. Cetuximab

6.1.4.2.1. Administration

Cetuximab should not be given as an intravenous push or bolus; instead, it should be administered by infusion pump or syringe pump at an infusion rate that should not exceed 10 mg/min. It should also be administered through a low protein binding 0.22-micrometer in-line filter. The parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and colorless and may contain a small amount of easily visible, white, amorphous, cetuximab particulates. Do not shake or dilute the solution.

6.1.4.2.2. Infusion Reactions

Serious infusion reactions requiring medical intervention and immediate, permanent discontinuation of cetuximab included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness,

myocardial infarction, and/or cardiac arrest. Severe (NCI CTCAE Grades 3 and 4) infusion reactions occurred in 8.4% of 1373 patients receiving cetuximab in 4 different clinical studies, with a fatal outcome in 1 patient (Cetuximab [Erbitux®] Prescribing Information, Appendix A). Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines.

Patients should be monitored for 1 hour following cetuximab infusion in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). If serious infusion reactions occur, study drug administration should be immediately interrupted and permanently discontinued. If hypersensitivity or infusion-related events develop, the infusion rate should be reduced by 50% for NCI CTCAE Grade 1 or 2 and non-serious NCI CTCAE Grade 3 infusion reactions. Patients who experience infusion reactions must be observed until resolution of the event.

6.1.4.2.3. Cardiopulmonary Arrest

Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients treated with radiation therapy and cetuximab as compared to none of 212 patients treated with radiation therapy alone (Cetuximab [Erbitux®] Prescribing Information, Appendix A). Carefully consider the use of cetuximab in combination with radiation therapy or platinum-based therapy with 5-FU in head and neck cancer patients who have a history of coronary artery disease, congestive heart failure, or arrhythmias in light of these risks. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after cetuximab infusion.

6.1.4.2.4. Pulmonary Toxicity

Interstitial lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (< 0.5%) patients receiving cetuximab in 3 clinical trials (Cetuximab [Erbitux®] Prescribing Information, Appendix A), as well as in other studies in colorectal cancer and head and neck cancer. Monitor patients for signs and symptoms of pulmonary toxicity and

interrupt cetuximab for acute onset or worsening of pulmonary symptoms and permanently discontinue cetuximab for confirmed ILD.

6.1.4.2.5. Dermatologic Toxicity

Dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example, S. aureus sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis occurred in patients receiving cetuximab therapy. Acneiform rash occurred in 82% of 1373 patients receiving cetuximab in 4 clinical trials (Cetuximab [Erbitux®] Prescribing Information, Appendix A). Severe acneiform rash occurred in 9.7% of patients.

Acneiform rash usually developed within the first 2 weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event continued beyond 28 days. Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing has also been observed in patients treated with cetuximab. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (e.g., Stevens-Johnson syndrome or toxic epidermal necrolysis). Prophylactic interventions for cetuximab skin rash using oral and/or topical antibiotics, sun block, moisturizing creams, or other agents may be instituted according to local standard of care. Possible oral antibiotic regimens for skin prophylaxis include oral doxycycline 100 mg twice-weekly or comparable regimens with tetracycline or minocycline. Patients will be monitored for dermatologic toxicities and infectious sequelae and they will be instructed to limit sun exposure during cetuximab therapy.

Recommended dose modifications for severe (NCI CTCAE Grade 3 or 4) acneiform rash are specified in Table 3.

Table 3. Cetuximab Dose Modification Guidelines for Rash

Severe Acneiform Rash	Cetuximab	Outcome	Cetuximab Dose Modification
First occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250 mg/m^2
		No Improvement	Discontinue cetuximab
Second occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 200 mg/m^2
		No Improvement	Discontinue cetuximab
Third occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 150 mg/m^2
		No Improvement	Discontinue cetuximab
Fourth occurrence	Discontinue cetuximab		

Source: Cetuximab (Erbitux®) Prescribing Information (Appendix A).

6.1.4.2.6. Hypomagnesemia and Electrolyte Abnormalities

In patients evaluated during clinical trials, hypomagnesemia occurred in 55% of 365 patients receiving cetuximab in one trial (Appendix A) and it was severe (NCI CTCAE Grades 3 and 4) in 6%–17%. In one study in which cetuximab was administered in combination with platinum-based therapy, the addition of cetuximab to cisplatin and 5-FU resulted in an increased incidence of hypomagnesemia (14% vs. 6%) and of Grade 3–4 hypomagnesemia (7% vs. 2%) compared to cisplatin and 5-FU alone. In contrast, the incidences of hypomagnesemia were similar for those who received cetuximab, carboplatin, and 5-FU compared to carboplatin and 5-FU (4% vs. 4%). No patient experienced Grade 3–4 hypomagnesemia in either arm in the carboplatin subgroup. The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to months after initiation of cetuximab. Periodically monitor patients for hypomagnesemia, hypocalcemia, and hypokalemia, during and for at least 8 weeks following the completion of cetuximab.

6.1.5. Specific Safety Management Guidelines

6.1.5.1. Cetuximab

Safety management guidelines for cetuximab are provided in (Cetuximab [Erbitux®] Prescribing Information, Appendix A).

6.1.5.2. Hu5F9-G4

6.1.5.2.1. Hemagglutination and Microangiopathy

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

AE Severity Grading for Hemagglutination and Microangiopathy

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

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

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

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

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

6.1.5.2.2. Anemia, Blood Cross-matching, and Packed Red Blood Cell Transfusion Procedures

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

During the Screening period prior to initiation of Hu5F9-G4 therapy, blood cell ABO phenotyping for minor antigens, type and screen (ABO/Rh), and Direct Antiglobulin Test (DAT) will be performed for each patient as described in Section 7.3.4. This, together with using the prior phenotype, will facilitate allocation of properly cross-matched blood, should a blood transfusion be warranted.

- Procedure for patients after exposure to Hu5F9-G4:
  1. ABO, Rh, and DAT may be pan-reactive due to Hu5F9-G4 binding to red cells. Therefore, if a non-urgent transfusion is ordered by the PI, perform the following procedures:

     - Front Type: EGA Treat cells (×2 Maximum) and Warm Wash × 4 (Minimum) with 0.9% Saline.
     - Back Type: Perform reverse anti-human globulin for both A and B.
     - If a valid ABO type cannot be obtained, mark the final report as invalid and notify the transfusion service for the site.

  2. Antibody screen

     If a pan-agglutinin/warm autoantibody is present in low ionic strength solution

(LISS), repeat the antibody screen with polyethylene glycol (PeG). Perform PeG adsorption studies and elution studies.

6.1.5.2.3. Blood Components for Transfusion

For all elective red cell transfusions, leucocyte-reduced units matched for the phenotype of the patients (as described above) will be used. Where exact matching for all the specified blood groups proves impractical (e.g., for MNS), 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.

6.1.5.2.4. Management of Hu5F9-G4 Infusion Reactions

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

- For Grade 1 infusion-related reactions, described as mild transient reaction, infusion interruption is not indicated, intervention is not indicated:
  - Remain at bedside and monitor patient until recovery from symptoms.

- For Grade 2 infusion-related reactions, 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 infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or 500-750 mg oral acetaminophen.
  - Remain at bedside and monitor patient until resolution of symptoms.
  - Corticosteroid therapy may also be given at the discretion of the Investigator.
  - If the infusion is interrupted, wait until symptoms resolve, then restart the infusion at 50% of the original infusion rate.
  - If no further complications occur after 60 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 will be administered at that visit.
  - Premedications should be considered before any future infusions.
  - The amount of Hu5F9-G4 infused must be recorded on the case report form (eCRF).
  - Patients who experience a Grade 2 infusion reaction during the post-infusion observation period that does not resolve during that time should be observed until the AE resolves or stabilizes, with vital sign measurements every 4 hours and additional evaluations as medically indicated for the management of the AE.

- For Grade 3 or Grade 4 infusion-related reactions, where Grade 3 is described as prolonged signs and symptoms (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion), or recurrence of symptoms

following initial improvement, or where hospitalization is indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates).

Grade 4 is described as having life-threatening consequences and where urgent intervention indicated.

- Immediately discontinue infusion of Hu5F9-G4.
- Begin an IV infusion of normal saline, and treat the patient as follows: Administer bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.
- The patient should be monitored until the Investigator is comfortable that the symptoms will not recur.
- Patients who have Grade 4 infusion reactions occurring with the first dose will be permanently discontinued from study treatment.
- Patients who experience Grade 3 infusion reactions must be given premedication prior subsequent doses. In this setting, premedication with oral acetaminophen (650 mg), oral or intravenous diphenhydramine (25-50 mg), and intravenous dexamethasone (4-20 mg), or a comparable regimen, is recommended.
- Patients who receive premedication and still have a Grade 3 or 4 infusion 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 infusion-related reactions 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).

6.1.5.2.5. Tumor Lysis Syndrome

In the case of evidence for tumor lysis syndrome associated with Hu5F9-G4, patients will be admitted to the hospital as clinically indicated. Standard

management will include vigorous IV hydration; correction of acidosis, if present; hypouricemic agents; and close monitoring of serum uric acid, phosphorus, and electrolytes. Study treatment should be held until the patient's condition resolves or stabilizes.

6.2. Post-therapy Follow-up and Patient Study Completion

Patients who complete, terminate, or decline further treatment should be encouraged to return for an End of Treatment Visit for evaluation of safety within 1 week of the decision to end Hu5F9-G4 treatment. The studies to be performed at end of treatment are listed in the Schedules of Assessments (SOAs), Section 7.4. It is strongly encouraged that patients return for their Safety Follow-up Visit 30 days (± 1 week) after the last dose of last study drug received. The Safety Follow-up Visit assessments are described in Section 7.5.

Patients are considered to have completed study drug treatment when they finish the Safety Follow-up Visit 30 days (± 1 week) after their last dose of the last study drug received, unless they are experiencing ongoing drug-related AEs and serious adverse events (SAEs). For patients being followed for ongoing AEs or SAEs, follow-up visits will continue at least every 4 weeks until resolution to baseline or stabilization of these events, unless the patient starts another anti-cancer therapy. Follow-up for ongoing AEs or SAEs after the Safety Follow-up Visit will stop if a patient begins another anti-cancer therapy.

All patients, including those who discontinue study treatment early, will be followed for response until progression and for survival for 5 years from the date of enrollment. For any patient who dies during this period, the cause of death must be reported to the Sponsor. Patients are considered to have completed study participation when they are no longer followed for disease progression or survival.

6.3. Defining the End of Trial

The end of the study for all patients occurs at the primary completion date, which is defined as the date on which the last patient completes follow-up for safety, disease progression, or survival, or when the CTSC decides to end the study.

Recruitment will cease when one of the following occurs:

- Study treatment is considered too toxic to continue treatment before the anticipated number of patients are recruited. This assessment will be made by the CTSC.
- The stated number of patients to be recruited is reached. This number may be increased to include replacement patients for those who are not DLT evaluable and patients added to intermediate dose or expanded cohorts as determined by the CTSC, and approved, if necessary, by the appropriate IRBs.
- The stated objectives of the trial are achieved.

In terminating the trial, the Sponsor and the Investigators must ensure that adequate consideration is given to the protection of the patient's interest.

7. STUDY EVALUATIONS

7.1. Schedules of Assessment for Phase 1b and Phase 2

Table 4 presents the SOA for the Phase 1b part of the study. The SOA for the Phase 2 part of the study is provided in Table 5. Unless otherwise noted procedures are to be completed prior to any study drug infusion. Table 6 shows post-treatment assessments for both phases of the study. Table 7 and Table 8 describes PK assessments for Phases 1b and 2, respectively. Table 9 describes the timing of correlative study sample collection and Table 10 provides details for CD47 receptor occupancy sampling for Phase 1b.

Table 4. Schedule of Assessments Phase 1b

Examination		Study 5F9004, Phase 1b: Phase 1b/2 Solid Tumor/CRC Patient Trial with Hu5F9-G4 + Cetuximab																								
Cycle (28-day cycles)		1							2						3				4				5+			
Cycle Day	SC	1	2	8	9	11	15	22	1	2	4	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22
Visit Window (Days)	-30	None		±1					±2	±1					± 2											
Assessments																										
Informed consent	X																									
Demographics	X																									
Medical and cancer history	X																									
Inclusion/exclusion criteria	X																									
Enrollment cohort assignment[a]	X																									
Serum or Urine Pregnancy Test	X	X[b]													X								Q8 W			
CBC with differential, platelets, reticulocytes[c]	X	X	X	X			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X		X	
Peripheral Blood Smear[d]	X	X[c]	X	X			X	X	X						X											
Serum chemistry[c]	X	X	X	X			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X		X	
Serum uric acid, phosphorous[c]	X	X	X	X			X																			

Examination		Study 5F9004, Phase 1b: Phase 1b/2 Solid Tumor/CRC Patient Trial with Hu5F9-G4 + Cetuximab																							
Cycle (28-day cycles)		1							2						3				4				5+			
Cycle Day	SC	1	2	8	9	11	15	22	1	2	4	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22
Visit Window (Days)	-30	None		±1					±2	±1					± 2											
Assessments																										
Haptoglobin, D-Dimer, thrombin time, and plasma fibrinogen[c]	X	X	X	X			X	X	X						X				X				X			
PT/INR, aPTT[c]	X			X					X						X				X				X			
Type and Screen (ABO/Rh), DAT[p]	X																									
Urinalysis[c]	X						X																			
Correlative studies[e]		X		X			X		X						X[q]											
Pharmacokinetics[f]		X		X	X	X	X	X	X	X	X	X	X	X	X	X			X				X[r]			
Antidrug Antibodies		X		X					X						X				X				X			
CD47 Receptor Occupancy[g]		X	X	X		X[l]	X	X	X			X			X				X				X[q,r]			
ECOG performance status	X	X		X			X	X	X						X				X				X			
Vital signs[h]	X	X	X	X		X[l]	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[i]	X	X[c]		X			X	X	X				X		X		X		X				X			
DLT Assessment[j]									X																	
Visual acuity	X	X[c]		X			X	X	X						X				X				X			

Examination		Study 5F9004, Phase 1b: Phase 1b/2 Solid Tumor/CRC Patient Trial with Hu5F9-G4 + Cetuximab																								
Cycle (28-day cycles)		1							2						3				4				5+			
Cycle Day	SC	1	2	8	9	11	15	22	1	2	4	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22
Visit Window (Days)	-30	None		±1					±2	±1					± 2											
Assessments																										
ECG[k]	X	X		X					X																	
PPD																										
Response assessment	X[t]														X[m]								Q8 W[n]			
Adverse events	→																									
Concomitant medications	→																									
Study Drug Administration																										
Cetuximab				X[o]			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hu5F9-G4 (Cohorts 1-4)		X		X			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hu5F9-G4 (Cohort 5)		X		X[l]		X[l]	X	X	X			X	X	X	X		X		X		X		X		X	

Abbreviations: ABO = any of the four blood groups A, B, AB, and O comprising the ABO system; aPTT = activated partial thromboplastin time; C = cycle number; CBC = complete blood count; DAT = direct antiglobulin test; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; PT = prothrombin time; Rh = Rhesus factor; RO = CD47 receptor occupancy; SC = Screening; W = weeks.

a. First dose of Hu5F9-G4 must be given within 30 days of all Screening tests.

Examination		Study 5F9004, Phase 1b: Phase 1b/2 Solid Tumor/CRC Patient Trial with Hu5F9-G4 + Cetuximab																							
Cycle (28-day cycles)		1							2						3				4				5+			
Cycle Day	SC	1	2	8	9	11	15	22	1	2	4	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22
Visit Window (Days)	-30	None		±1					±2	±1					± 2											
Assessments																										

b. May use Screening pregnancy test performed within 72 hours of first dose.
c. Pre-infusion assessments may be performed up to 72 hours before study drug treatment.
d. Peripheral blood smear slides from Cycle 1 will be retained and sent to the Sponsor for storage. Collection details are provided in Section 7.3.5.
e. Refer to Table 9 for correlative studies timepoint details.
f. Refer to Table 7 for PK timepoint details.
g. Refer to Table 10 for RO timepoint details.
h. Prior to infusion and within 30 minutes after each infusion (if applicable). Details about data to be collected are provided in Section 7.3.2.
i. Full physical examination at Screening, symptom-directed PE thereafter.
j. DLT will be assessed through the first 4 weeks of the study.
k. Single at Screening. Triplicate within 2 hours prior to cetuximab infusion and within 30 minutes of the end of Hu5F9-G4 infusion on treatment for Phase 1b only.
l. Loading Dose Cohort only: Doses of Hu5F9-G4 administered on Day 8 and 11 may be shifted by ± 1 day, provided that doses are not administered on consecutive days.
m. (± 1 week) Efficacy assessment details are provided in Section 7.9.
n. After Cycle 3, the adjustment window is ± 2 weeks.
o. From 30 to 60 minutes prior to administration of the first dose of cetuximab, patients should be premedicated with an H1 antagonist (e.g., 50 mg of diphenhydramine) intravenously.
p. Detailed guidance is provided in Section 7.3.4.
q. To be performed with response assessment (± 1 week from Cycle 3, Day 1).
r. Starting with Cycle 5, samples to be collected every other cycle (e.g., Cycle 5, 7, 9, and so on).
s. PPD
t. Historic imaging may be used for screening diagnostic imaging if performed within 30 days of the first dose of Hu5F9-G4; details are provided in Section 10.
u. Archival tumor tissue may be collected by the sponsor for correlative studies. The tissue block is preferred, but if not available at least 10 unstained slides are suggested.

Table 5. Schedule of Assessments Phase 2

Examination		Study 5F9004, Phase 2: P1b/2 Solid Tumor/CRC Trial of Hu5F9-G4 + Cetuximab																						
Cycle (28-day cycles)		1							2				3				4				5+			
Cycle Day	SC	1	2	8	9	11	15	22	1	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22
Visit Window (Days)	-30	None		±1					±2		±1		± 2											
Assessments																								
Informed Consent	X																							
Demographics	X																							
Medical and Cancer History	X																							
Inclusion/Exclusion Criteria	X																							
Enrollment Cohort assignment[a]	X																							
Serum or Urine Pregnancy Test	X	X[b]											X								Q8 W			
CBC w differential, platelets, reticulocytes[c]	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Peripheral Blood Smear[d]	X	X[c]	X	X			X	X	X				X											
Serum chemistry[c]	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Serum uric acid, phosphorous[c]	X	X	X	X			X																	
Haptoglobin, D-Dimer, thrombin time, and plasma fibrinogen[c]	X	X	X	X			X	X	X				X				X				X			
PT/INR, aPTT[c]	X			X					X				X				X				X			
Type and Screen (ABO/Rh), DAT	X[p]																							

Examination		Study 5F9004, Phase 2: P1b/2 Solid Tumor/CRC Trial of Hu5F9-G4 + Cetuximab																						
Cycle (28-day cycles)		**1**							**2**				**3**				**4**				**5+**			
Cycle Day	**SC**	**1**	**2**	**8**	**9**	**11**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**		**±1**		**± 2**											
Assessments																								
Urinalysis[c]	X						X																	
Correlative studies[e]		X							X				X[q]											
Pharmacokinetics[f]		X		X			X		X	X	X		X				X				X			
Antidrug Antibodies		X		X					X				X				X				X			
CD47 Receptor Occupancy[g]																								
ECOG performance status	X	X		X			X	X	X				X				X				X			
Vital signs[h]	X	X	X	X		X[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[i]	X	X[c]		X			X	X	X		X		X		X		X				X			
Visual acuity	X	X[c]		X			X	X	X				X				X				X			
ECG[k]	X																							
PPD																								
Response assessment	X[s]												X[m]								Q8W[n]			
Adverse events	→																							→
Concomitant medications	→																							→
Study Drug Administration																								
Cetuximab administration				X[o]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hu5F9-G4 administration[t]		X		X			X	X	X		X		X		X		X		X		X		X	

Examination		Study 5F9004, Phase 2: P1b/2 Solid Tumor/CRC Trial of Hu5F9-G4 + Cetuximab																						
Cycle (28-day cycles)		1							2				3				4				5+			
Cycle Day	SC	1	2	8	9	11	15	22	1	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22
Visit Window (Days)	-30	None		±1					±2		±1		± 2											
Assessments																								

Abbreviations: ABO = any of the four blood groups A, B, AB, and O comprising the ABO system; aPTT = activated partial thromboplastin time; C = cycle number; CBC = complete blood count; DAT = direct antiglobulin test; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; PT = prothrombin time; Rh = Rhesus factor; SC = Screening; W = weeks.

a. First dose of Hu5F9-G4 must be given within 30 days of all Screening tests.
b. May use Screening pregnancy test performed within 72 hours of first dose.
c. Pre infusion assessments may be performed up to 72 hours before study drug treatment.
d. Peripheral blood smear slides from Cycle 1 will be retained and sent to the Sponsor for storage. Details are provided in Section 7.3.5.
e. Refer to Table 9 for Correlative studies timepoint details.
f. Refer to Table 8 for PK timepoint details.
g. Beginning with Protocol Amendment 3, samples for receptor occupancy will not be collected in the Phase 2 part of the study.
h. Prior to infusion and within 30 minutes after each infusion (if applicable). Details are provided in Section 7.3.2.
i. Full physical examination at Screening, symptom directed PE thereafter.
j. This is a placeholder from Phase 1; this footnote does not appear in the Phase 2 SOA.
k. Single at Screening. Triplicate within 2 hours prior to infusion and within 30 minutes of the end of infusion on treatment for Phase 1b only.
l. Loading Dose Cohort only: Doses of Hu5F9-G4 administered on Day 8 and 11, may be shifted by ± 1 day, provided that doses are not administered on consecutive days.
m. (± 1 week) Efficacy assessment details are provided in Section 7.9.
n. After Cycle 3, the adjustment window is ± 2 weeks.
o. From 30 to 60 minutes prior to administration of the first dose of cetuximab, patients should be premedicated with an H1 antagonist (e.g., 50 mg of diphenhydramine) intravenously.
p. Detailed guidance is provided in Section 7.3.4.
q. To be performed with response assessment (± 1 week from Cycle 3, Day 1).
r. PPD
s. Historic imaging may be used for screening diagnostic imaging if performed within 30 days of the first dose of Hu5F9-G4; details are provided in Section 10.

Examination		Study 5F9004, Phase 2: P1b/2 Solid Tumor/CRC Trial of Hu5F9-G4 + Cetuximab																					
Cycle (28-day cycles)		1							2				3				4				5+			
Cycle Day	SC	1	2	8	9	11	15	22	1	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22
Visit Window (Days)	-30	None		±1					±2		±1		± 2											
Assessments																								

t Per CTSC, alternate Phase 2 doses and schedules may include additional Hu5F9-G4 dosing time points.

u. Archival tumor tissue may be collected by the sponsor for correlative studies. The tissue block is preferred, but if not available at least 10 unstained slides are suggested.

Table 6. Post-treatment Assessments, Phase 1b and Phase 2

Examination	Study 5F9004, Post-treatment Assessments: Phase 1b/2 Solid Tumor/CRC Trial of Hu5F9-G4 + Cetuximab			
Cycle (28-day cycles)	**End of Treatment**	**Safety Follow-up**	**Long-term Follow-up**	**Survival Follow-up**
	Within 1 Week of EOT Decision	**30 Days after Last Dose of study drug**	**Until disease progression or new anti-cancer therapy**	**Up to 60 months from date of LPE**
Visit Window		**± 1 Week**	**± 2 Weeks**	**± 1 Month**
Assessments				
Serum or urine pregnancy test		X		
CBC w differential, platelets, reticulocyte count		X		
Peripheral blood smear		X		
Serum chemistry		X		
Haptoglobin, D-Dimer, thrombin time, and plasma fibrinogen		X		
PT/INR, aPTT		X		
Pharmacokinetics	X[a]	X[a]		
Correlative studies	X		X[b]	
Antidrug Antibodies	X	X		
CD47 Receptor Occupancy	X[c]			
ECOG performance status		X		
Vital signs		X		
Physical examination (symptom directed)		X		
PPD				
Response assessment	X[e]	X[d,e]	Q8W[b]	
Adverse events	X	X	Q4W[b]	
Concomitant medications	X	X		
Survival follow-up and new anti-cancer therapy				Q3M

Abbreviations: aPTT = activated partial thromboplastin time; CBC = complete blood count; CRC = colorectal cancer; DLT = dose-limiting toxicity; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment Visit; INR = international normalized ratio; LPE = last patient enrolled; M = month(s); PT = prothrombin time' W = week(s).

a. Required only in Phase 1b.
b. Details provided in Section 7.6.
c. Sample to be collected only if the visit occurs prior to Cycle 2. Samples are collected only for Phase 1b, Cohorts 1 to 4.
d. Required only if not completed within the 4 weeks prior to the Safety Follow-up Visit.
e. Details provided in Section 10.

Table 7. Pharmacokinetic Assessments, Phase 1b

Phase 1b	Cycle 1						Cycle 2						Cycle 3		C4-C5	C7+	EOT	SFU
Day	**1**	**8**	**9**	**11**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**1**	**1**	**—**	**—**
Before cetuximab infusion (within 12 hr)		X			X	X	X						X	X	X[a]		X	X
Before Hu5F9-G4 infusion (within 12 hr)	X	X[b]			X[b]	X[b]	X[b]			X[b]	X[b]	X[b]	X[b]	X[b]	X[a,b]	X[a]	X	X
1 hr (± 15 min) after Hu5F9-G4 infusion	X	X			X	X	X			X			X	X	X[a]	X[a]		
24 hr (± 8 hr) after Hu5F9-G4 infusion (Cycle 1 Day 8 or Cycle 2 Day 1)			X					X										
72 hr (± 12 hr) after Hu5F9-G4 infusion (Cycle 1 Day 8 or Cycle 2 Day 1)				X[c]					X									
1 hr (± 15 min) after cetuximab infusion		X					X						X		X[a]			

Abbreviations: C = cycle; EOT = End of Treatment Visit; hr = hour(s); min = minute(s); SFU = Safety Follow-up Visit.

a Starting with Cycle 5, samples to be collected every other cycle (e.g., Cycle 5, 7, 9, and so on).

b. Hu5F9-G4 sample may be collected before the cetuximab infusion at same time as “pre-cetuximab infusion” PK timepoint.

c Sample to be collected before Hu5F9-G4 dose when applicable to Loading Dose Cohort.

Table 8. Pharmacokinetic Assessments, Phase 2

Phase 2	Cycle 1			Cycle 2			C3	C4	C5+
Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**
Before cetuximab infusion (within 12 hr)		X		X		X	X	X	X[a]
1 hr (±15 min) after cetuximab infusion		X	X	X			X	X	X[a]
Before Hu5F9-G4 infusion (within 12 hr)	X	X[b]	X[b]	X[b]		X	X[b]	X[b]	X[a,b]
1 hr (±15 min) after Hu5F9-G4 infusion	X	X	X	X		X	X	X	X[a]

Abbreviations: C = cycle; hr = hour(s); min = minute(s).
Note: If at any point in the study the CTSC determines that sufficient PK data have been generated, it may halt the collection of PK samples.
a. Starting with Cycle 5, samples to be collected every fourth cycle (e.g., Cycle 5, 9, 13, end of treatment, and survival follow-up).
b. Hu5F9-G4 sample may be collected before the cetuximab infusion at same time as "pre-cetuximab infusion" PK timepoint.

Table 9. Correlative Studies Sample Time Points, Phases 1b and 2

Time Points	Cycle 1			Cycle 2	Cycle 3	EOT	LTFU
Day	**1**	**8**	**15**	**1**	**1**		
Phase 1b							
Pre-study drug infusion [a,b]	X	X	X	X	X[c]		
1 hour (± 15 min) after Hu5F9-G4 infusion	X	X	X				
Phase 2							
Pre-study drug infusion [a,b]	X			X	X[c]		
1 hour (±15 min) after Hu5F9-G4 infusion	X						
Phase 1b and Phase 2						X[d]	X[e]

Abbreviations: EOT = End of Treatment Visit; LTFU = long-term follow-up; min = minute(s).
a. Sample to be collected before cetuximab infusion when applicable.
b. Pre-infusion laboratory tests may be collected up to 72 hours before study drug treatment.
c. To be performed with response assessment (± 1 week from Cycle 3, Day 1).
d. Sample to be collected within 1 week of EOT decision.
e. Obtained at the time of disease progression, or the start of a new anti-cancer therapy.

Table 10. CD47 Receptor Occupancy Sample Time Points, Phase 1b, Cohorts 1 to 4

Time Points	Cycle 1						Cycle 2		C3	C4+	EOT
Day	**1**	**2**	**8**	**11**	**15**	**22**	**1**	**8**	**1**	**1**	**—**
Pre-study drug infusion	X		X[a]	X[b]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a,c]	X[d]
1 hr (± 15 min) after Hu5F9-G4 infusion	X		X	X[b]	X	X			X	X[c]	
24 hr (± 8 hr) after Hu5F9-G4 infusion on Day 1		X									
72 hour (± 8 hr) after Hu5F9-G4 infusion on Day 8[e]				X							

Abbreviations: C = cycle; EOT = End of Treatment Visit; hr = hour(s); min = minute(s).

a. Sample to be collected before cetuximab infusion when applicable.
b. Samples to be collected from patients in the loading dose cohort only.
c. Starting with Cycle 5, samples to be collected every other cycle (e.g., Cycles 5, 7, 9, and so on).
d. Sample to be collected only if the visit occurs prior to Cycle 2.
e Sample to be collected from patients in non-loading dose cohort(s) only.

7.2. Assessment by Study Period

7.2.1. Screening Assessments

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

- Confirmation that the Informed Consent Form has been signed and consent process has been documented.
- Confirmation that all inclusion/exclusion criteria have been met.
- Demographic data including sex, date of birth, age, race, and ethnicity.
- Vital signs: blood pressure, pulse, respiration, temperature, height and weight.
- Physical examination (complete) and ECOG (Appendix C).
- Visual acuity assessment by Snellen eye chart or comparable eye chart.
- Single ECG.
- Relevant medical and cancer history will be completed through consent (all findings recorded on the medical history electronic case report form [eCRF]).
- Documentation of concomitant and prior medications.
- Adverse Events related to Screening procedures and any SAEs reporting.
- Serum or urine pregnancy test (in women of childbearing potential).
- Local laboratory values, including CBC (with differential, platelets, reticulocyte count), serum chemistry, serum uric acid, phosphorous, haptoglobin, D-dimer, thrombin time, plasma fibrinogen, PT/INR, aPTT, and urinalysis. (See .)
- Local laboratory Type and Screen (ABO/Rh) and DAT. (Details are provided in Section 7.3.4).
- Local laboratory Peripheral Blood Smears. (Details are provided in Section 7.3.5).
- ECOG performance status.
- Tumor biopsy (within 2 weeks prior to first dose of drug): strongly encouraged for Phase 1b, mandatory for Phase 2. Archival tumor tissue may be collected by the sponsor for correlative studies. The tissue block is preferred, but if not available at least 10 unstained slides are suggested.
- Response assessment: diagnostic imaging. (Historic imaging may be used for

screening if performed within 30 days of the first dose of Hu5F9-G4; details are provided in Section 10).

- Tumor molecular profile if available including: Microsatellite Instability status (MSI-High, MSI-Low, MSI-Stable, or unknown), Primary tumor sidedness (Left, Right, or unknown), BRAF V600E mutation (Yes, no, or unknown), KRAS mutation status (wild-type, mutant or unknown), NRAS status (wild-type, mutant, or unknown), PIK3CA mutation analysis (yes, no, or unknown).

Screening assessments will be completed within a 30-day Screening period prior to the enrollment. Screening assessments may be repeated during the 30-day Screening period. Screening assessments may be used for Cycle 1, Day 1 dosing if performed within 72 hours of study drug administration. Assessments performed as part of standard of care prior to ICF may be used if they are within the 30-day Screening period.

7.3. Description of Study Procedures

Refer to SOA Table 4 through for timing of study procedures.

7.3.1. Physical Examination/Visual Acuity

Complete physical exam should be performed at Screening. Thereafter, symptom-directed physical exams are acceptable and may also include routine examination of the skin (including fingers, toes, and ears) and CNS. For patients who have a change in visual acuity of 3 lines or more on a Snellen chart or comparable eye chart, an ophthalmologist should be consulted for additional evaluation.

7.3.2. Vital Signs

Vital signs should include heart rate, respiratory rate, blood pressure, temperature, and weight. Height should be recorded during Screening only. Weight should be recorded during Screening and on Day 1 of each cycle.

7.3.3. Electrocardiographs

One ECG will be performed at screening. Triplicate ECGs will be performed before the cetuximab dose (within 2 hours of infusion) and within 30 minutes of the end of Hu5F9-G4 infusion for Phase 1b only.

7.3.4. Type and Screen (ABO/Rh), DAT

Due to the risk of developing anemia, blood phenotyping, type and screen (ABO/Rh), and direct antiglobulin test (DAT) should be performed at Screening prior to exposure to Hu5F9-G4: Full phenotyping (if not transfused in last 3 months) – ABO, Rh, D, C, E, Kell, Kidd, Duffy, MNS, and antibody screen. Treatment with Hu5F9-G4 may make phenotyping difficult due to expected coating of the RBC membrane. In addition, patients who experience a drop in hemoglobin to below 9 g/dL at any time, or patients in whom clinical findings indicate a possible need for transfusions, it is recommended, but not required, that a Type and Screen and DAT be performed. Details are provided in Table 11.

7.3.5. Peripheral Blood Smear Assessment

Peripheral smears will be collected prior to selected study drug infusions and assessed for the presence of hemagglutination, in addition to standard cell morphology assessment. Slides should be processed and assessments should occur in accordance with the local laboratory's standard reporting timelines. These samples should be collected from the arm contralateral to the arm being used for drug infusion, if possible. Peripheral smears will be evaluated according to the guidelines provided in Appendix E. For patients undergoing blood transfusion, samples for peripheral smears will be collected 1 hour (± 30 minutes) after completion of the transfusion. PPD

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7.3.6. Pregnancy Test

Pregnancy tests are required only for women of childbearing potential (excluding patients who are post-menopausal with absence of menses for at least 1 year and/or surgically sterilized). A urine or serum pregnancy test is required at Screening and within 72 hours prior to dosing on Day 1. The Day 1 pregnancy test does not need to be repeated if the Screening pregnancy test was done within the 72 hours prior to dosing. Pregnancy tests will be obtained every 8 weeks.

7.3.7. Adverse Events

At each visit all AEs observed by the Investigator or reported by the patient that occur after the first dose of study drugs through 30 days after the last dose of study drugs are to be reported using the applicable electronic case report form (eCRF; Section 9.3.1). AEs that occur prior to assignment of study treatment that are assessed as related to a protocol-mandated intervention (e.g., invasive procedures such as biopsies) must also be reported.

Following 30 days after the last dose of investigational product, Investigators should report any SAEs they assess as related to Hu5F9-G4 or cetuximab.

7.3.8. Concomitant Medications

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

7.4. End of Treatment Visit

End of Treatment Visit to be completed within 1 week of the decision to end treatment with Hu5F9-G4.

- Pharmacokinetic sample collection (for Phase 1b only). PK samples will be collected for Hu5F9-G4 and cetuximab.
- Correlative Studies
- Antidrug Antibodies
- CD47 Receptor Occupancy (only if End of Treatment Visit occurs prior to Cycle 2).
- Response Assessment, if not performed within the last 4 weeks. (Details are provided in Section 10)
- Adverse Events
- Concomitant medications

7.5. Safety Follow-up Visit

Safety Follow-up visit to be completed within 30 days (± 1 week) after the last dose of Hu5F9-G4.

- Local Laboratory
  - CBC (w differential, platelets, reticulocyte count)
  - Serum chemistry
  - Haptoglobin, D-Dimer, thrombin time, and plasma fibrinogen
  - PT/INR, aPTT
- Local laboratory Peripheral Blood Smear
- Serum or urine pregnancy test (in women of childbearing potential)
- Pharmacokinetic sample collection for Hu5F9-G4 and cetuximab
- Antidrug Antibodies
- ECOG performance status Appendix C
- Vital signs
  - blood pressure
  - pulse
  - respiration
  - temperature
  - weight

- Adverse Events
- Concomitant medications
- Physical examination (symptom-directed)
- Response Assessment (± 1 week), if not performed within the last 4 weeks (Section 10)

7.6. Long-term Follow-up

Patient will be followed until disease progression or until they begin a new anti-cancer therapy.

- Response assessment (± 1 week), every 8 weeks (Section 10)
- Correlative studies

For patients who achieve a partial or complete response while on study, a repeat disease assessment will be obtained at the time of disease progression whenever possible. These assessments include:

- Blood sample for correlative studies
- PPD

Following the Safety Follow-up Visit, patients with ongoing drug-related AEs and SAEs will be followed for safety. If any study drug-related AEs or SAEs are ongoing after the Safety Follow-up Visit, follow-up with the patient will occur at least every 4 weeks until resolution to baseline or stabilization of these events, unless the patient starts another anti-cancer therapy. Follow-up will stop when a patient begins another anti-cancer therapy.

7.7. Survival Follow-up

All patients who permanently discontinue all study treatment for disease progression (according to the RECIST Version 1.1 Criteria; Section 10), clinical progression, unacceptable toxicity, partial withdrawal of consent, or administrative decision, will be contacted during a clinic visit or by telephone to assess survival, disease progression (if not documented previously), and the commencement of new cancer therapy following the last administration of study drugs. Patients will be contacted

every 3 months (± 1 month) from the date of the safety follow-up visit, until 60 months from the date that the last patient is enrolled into the study or full withdrawal of consent. For any patient who dies during this period, the cause of death must be reported to the Sponsor. The patient's primary physician or family may be contacted by the investigator to obtain survival information in case the patient cannot be reached. Public records may also be used to obtain survival information if the patient cannot be reached.

7.8. Safety Assessments

Analytes to be assessed by the local laboratory or specialty laboratories are presented in Table 11.

Table 11. Analyte Listing

Chemistry	Hematology	Urinalysis	Type and Screen (ABO/Rh), Direct Antiglobulin Test	Other Laboratory Measurements
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine Uric acid Total bilirubin Direct bilirubin LDH AST (SGOT) ALT (SGPT) Alkaline phosphatase	RBC Hemoglobin Hematocrit Platelets WBC Differential • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes Reticulocytes Haptoglobin D-Dimer Thrombin Plasma fibrinogen PT, aPTT, and INR Peripheral Blood Smear • Spherocytes • RBC Fragments/Schistocytes • RBC Agglutination • Nucleated RBCs	RBC Glucose Protein Urine pH Ketones Bilirubin Urine specific gravity Blood	ABO Rh Blood Group System • Rh D Factor • Rh C Factor • Rh E Factor • Rh c Factor • Rh e Factor Kell Antigen Kidd Antigen Duffy Antigen MNS Blood Group • M +/- • N +/- • S +/- • s +/- DAT	Serum or Urine Pregnancy Correlative studies [a] Pharmacokinetics [a] CD47 Receptor Occupancy [a,b] ADAs [a]

	• RBC abnormalities • Platelet Aggregation			

Note: Refer to Section 7.1 Schedule of Assessment tables for collection time points.
Abbreviations: ABO = any of the four blood groups A, B, AB, and O comprising the ABO system; ACTH = adrenocorticotropic hormone; ADA = anti-drug antibody; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DAT = direct antiglobulin test; FSH = follicle-stimulating hormone; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell; Rh = Rhesus factor; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; T4 = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cells.
a. These assays may be performed at a specialty laboratory.
b. Beginning with Protocol Amendment 3, these samples will no longer be collected.

7.9. Efficacy Assessments

Appropriate cancer staging assessments should be performed. Imaging assessments are to be conducted according to the RECIST Version 1.1 Criteria for solid tumors (Section 10.1; Appendix D) and iRECIST (Seymour 2017). The same imaging modality used at Screening should be used throughout the study whenever possible. It is understood that some circumstances may require a different imaging modality. An alternate imaging modality is acceptable and may be performed at the Investigator's discretion.

The first response assessment will occur at Cycle 3, Day 1 (± 1 week). After Cycle 3, assessments will have a window of ±2 weeks. Subsequent response assessments will occur every 2 cycles. Response assessment will be obtained at treatment termination, unless a prior radiographic assessment has been performed within the prior 4 weeks or a prior response assessment documented PD (progressive disease).

7.10. Immunogenicity

Peripheral blood for immunogenicity assessments for antidrug antibodies against Hu5F9-G4 will be collected on Days 1 and 8, and then on Day 1 of all subsequent cycles; at the End of Treatment Visit; and at the Safety Follow-up Visit. When collected on the day of study drugs dosing, the blood sample must be collected before dose administration. A precise, sensitive, and reproducible qualitative electrochemiluminescent (ECL) assay will be used to measure antibodies to Hu5F9-G4 in serum samples. This assay has been validated in cynomolgus monkey serum and has been used for the IND-enabling non-human-primate toxicology study for Hu5F9-G4 (PR013/20044845) and in Phase 1 clinical trials with Hu5F9-G4 (Studies SCI-CD47-001 and SCI-CD47-002). For patients who have tested positive for antidrug antibodies (ADA), the impact of ADA on PK, safety, and biologic activity will be assessed. Neutralizing antibodies to Hu5F9-G4 will also be assessed for patients who test positive for ADA. Antidrug antibodies to cetuximab may be assessed if the CTSC or Sponsor determines such testing is needed.

7.11. Pharmacodynamic and Biomarker Assessments

CD47 Receptor Occupancy

Testing for CD47 receptor occupancy on select target cells enables pharmacodynamic testing of Hu5F9-G4 to inform both safety and efficacy parameters. First, the degree of saturation of CD47 receptors on red blood cells serves as a pharmacodynamic assessment for degree of anemia. Second, CD47 receptor occupancy on WBCs and circulating or bone marrow-resident lymphoma cells provides information on level of CD47 saturation of the internal CD47 tissue sink and drug exposures on tumor cells, respectively. Samples for CD47 Receptor Occupancy studies in the peripheral blood will be collected as described in the schedule of assessments (Section 7.1) and were planned for both the Phase 1b and Phase 2 parts of the study. Beginning with Protocol Amendment 3, and with approval from the CTSC, CD47 receptor occupancy studies were removed from the Phase 2 assessments.

Correlative Blood Samples

Correlative studies will be performed on peripheral blood samples to determine the biologic activity of Hu5F9-G4 in combination with cetuximab on circulating immune cells. These studies that may include, but are not limited to, investigations in plasma cytokine levels, characterization of circulating T cells, and other studies. Where applicable, blood samples will be collected as described in Table 9. If at any point in the study the CTSC determines that sufficient correlative data have been generated, it may halt the collection and analysis of these samples.

Tumor Biopsies

Tumor biopsies will be obtained during both the Phase 1b and Phase 2 parts of the study. PPD . For the Phase 2 part, tumor biopsies are mandatory, unless the Investigator determines that it is not feasible. These reasons could include, but are not limited to, lack of accessible tumor tissue to biopsy and patient safety issues. A tumor biopsy will be obtained prior to treatment (within 2 weeks before the first dose of drug) and on Cycle 2 Day 8

(± 2 weeks). Core biopsies may be collected for these timepoints; however excisional biopsies, where possible, are preferred over core biopsies. Archival tumor tissue may be collected by the sponsor for correlative studies. The tissue block is preferred, but if not available at least 10 unstained slides are suggested.

In addition, for patients who achieve a partial or complete response while on study, a repeat tumor biopsy will be collected at the time of disease progression, whenever possible. PPD

8. STUDY DISCONTINUATION

8.1. Withdrawal of Patients from Study Drug Treatment

Patients (or a legally acceptable representative) may decline to continue receiving study drugs at any time during the study. The patient's health and welfare is the primary consideration in any determination to discontinue study drugs treatment. Patients who withdraw from study drugs during the treatment period should be encouraged to return for an End of Treatment Visit for evaluation of safety within 1 week of the decision to end Hu5F9-G4 treatment. The studies to be performed at end of treatment are listed in the Schedules of Assessments, Section 7.1. It is strongly encouraged that patients return for their Safety Follow-up Visit 30 days (± 1 week) after their last dose of study drugs. The Safety Follow-up Visit assessments are described in Table 6. All patients who withdraw from study drugs treatment will be followed for disease response and survival.

Reasons for patient withdrawal from study drugs treatment may include, but are not limited to, the following:

- Tumor progression, including confirmed tumor progression according to iRECIST
- Unacceptable toxicity
- Clinically significant change in the patient's status that precludes further treatment (e.g, pregnancy or other AE)
- Patient's request, with or without a stated reason
- Investigator or treating physician decision in the absence of any of the above.

8.2. Withdrawal of Patients from Study

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

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

Reasons for patient withdrawal from the study may include, but are not limited to, the following:

- Death
- Withdrawal of consent
- Lost to follow up
- Study termination

8.3. Study Termination

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

9. ASSESSMENT OF SAFETY

9.1. Safety Parameters and Definitions

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

Forty Seven Inc. or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating Investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive, and/or local regulatory requirements.

9.1.1. Adverse Event

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

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies).
- AEs that occur prior to administration of the study drug that are related to a protocol-mandated intervention (e.g., invasive procedures such as biopsies).
- Preexisting medical conditions, judged by the Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

9.1.2. Serious Adverse Event

An SAE is any AE that at any dose is:

- Fatal (i.e., the AE is the actual cause of death)

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

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

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

9.2. Methods and Timing for Capturing and Assessing Safety Parameters

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

9.2.1. Adverse Event Reporting Period

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

After initiation of any the study drugs, all AEs and SAEs regardless of attribution will be collected until 30 days following the last dose of the last study drug received or the Safety Follow up Visit (whichever is later), or when the patient begins an alternate anti-cancer therapy.
At any time, even after 30 days after the last dose of the last study drug received or the Safety Follow up Visit, Investigators are to report SAEs that they assess to be related to one of the study drug (Hu5F9-G4 and/or cetuximab received as part of this study).
The Investigator must follow all unresolved SAEs and study drug-related AEs until the events are resolved (back to baseline) or stabilized, are determined to be irreversible by the Investigator, the Medical Monitor deems it necessary after the end of the study, the patient initiates alternate therapy for their cancer, or the patient is lost to follow-up. Resolution of AEs and SAEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification (SDV).

The Sponsor or its designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details (e.g., hospital discharge summary, consultant report, or autopsy report) deemed necessary to appropriately evaluate the SAE report.

9.2.2. Eliciting Adverse Events

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

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

9.2.3. Assessment of Severity and Causality of Adverse Events

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

For each AE and SAE recorded on the applicable eCRF, the Investigator will make an assessment of seriousness, severity, and causality (seriousness criteria are provided in Section 9.1.2.). A causality assessment will be made for both Hu5F9-G4 and cetuximab individually.

The AE grading (severity) scale (Appendix B) will be used for AE reporting and Table 12 provides additional guidance for AEs not specifically mentioned in CTCAE. Table 13 provides guidance for assessing the causal relationship to the study drug(s).

Table 12. Adverse Event Grade (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Transient or mild discomfort (<48 hours); no interference with the patient's daily activities; no medical intervention/therapy required
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a].	Mild-to-moderate interference with the patient's daily activities; no or minimal medical intervention/therapy required
3	Severe (apply event-specific NCI CTCAE grading criteria) Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL[b].	Considerable interference with the patient's daily activities; medical intervention/therapy required; hospitalization possible
4	Life-threatening consequences; urgent intervention indicated.	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable
5	Death related to adverse event	

Abbreviations: ADL = activities of daily living; AE = adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Source: NCI CTCAE, Version 4.03 (Appendix B)
Notes: Use the alternate descriptions for Grade 1, 2, 3, and 4 events when the observed or reported AE does not appear in the NCI CTCAE listing. A Semi-colon indicates 'or' within the description of the grade. A single dash (-) indicates a grade is not available.
a. Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

To ensure consistency of causality assessments, Investigators should apply the following general guidelines:

Table 13. Causal Attribution Guidance

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

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

9.3. Procedures for Recording Adverse Events

9.3.1. Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs on the eCRF. Colloquialisms and abbreviations should be avoided.

A separate log line in the Adverse Event eCRF should be used for each medical concept that needs to be recorded.

9.3.1.1. Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE on separate log lines of the eCRF. If a diagnosis is subsequently established, it should

be reported to Forty Seven Inc. by subsuming the symptoms under the diagnosis and according to the eCRF Completion Guidelines .

9.3.1.2. Adverse Events Occurring Secondary to Other Events

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

9.3.1.3. Persistent or Recurrent Adverse Events

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

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

9.3.1.4. Abnormal Laboratory Values

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

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

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

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

9.3.1.5. Deaths

All deaths that occur during the protocol-specified AE reporting period (Section 9.2.1), regardless of attribution, will be recorded on an eCRF and expeditiously reported to the Sponsor within 24 hours of awareness and not later than the next business day. This includes death attributed to progression of disease.

If the death is attributed to progression of disease, particularly in the absence of other signs and symptoms, record "[specific tumor type] progression" as the SAE term on the SAE Report Form.

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

9.3.1.6. Worsening of Disease

Worsening of and/or progression of disease should not routinely be recorded as an AE or SAE if it does not result in death. These data will be captured as efficacy assessment data. However, worsening and/or progression of disease should be

recorded as an SAE if the outcome is fatal in the absence of other signs and symptoms (Section 9.3.1.5), or if the Investigator assesses the disease progression to be related to one of the study drugs.

9.3.1.7. Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless it is a planned hospitalization or prolonged hospitalization to:

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

9.3.1.8. Other Reportable Information

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

Pregnancy

Any pregnancy occurring in a patient or a patient's partner during treatment with either study drug or within 6 months of last study drugs administration must be reported (Section 9.4.2) within 24 hours of becoming aware of it, using a Pregnancy Notification Form (provided in the Investigator Trial File). If the pregnancy occurs in a patient's partner, the Investigator must obtain consent from the patient's partner before collecting any pregnancy-related information. All pregnancies must be followed up until there is a pregnancy outcome using a pregnancy outcome form. In the event that the neonate/s has/have abnormalities at birth, additional data will be collected regarding the abnormalities. Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to any of the

study drugs should be recorded and reported as an SAE within 24 hours of awareness (Section 9.4.2).

Spontaneous or therapeutic abortion should always be reported as an SAE (medically significant event) and recorded on a Serious Adverse Event Report Form, and expeditiously reported to the Sponsor as described in (Section 9.4.2).

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

- Bilateral tubal occlusion
- Vasectomized partner
- Intra-uterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Oral combined hormonal contraception (estrogen and progestogen containing) associated with inhibition of ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Abstinence

  Defined as: refraining from heterosexual intercourse for the entire period of risk associated with the study treatments. Periodic abstinence is not acceptable (calendar, symptothermal, post-ovulation methods), nor is the withdrawal method (coitus interruptus). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Contraception must be effective at the first administration of any of the study drugs, throughout the trial, and for 6 months after the last dose of cetuximab or 4 months after the last dose of Hu5F9-G4, whichever occurs later.

Male patients, who are sexually active with partners of child-bearing potential and have not had a vasectomy, must agree to take measures not to father children by using one acceptable method of contraception such as condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository during the study.

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

Male patients must also refrain from sperm donation from the administration of the first dose of Hu5F9-G4, throughout the trial, and for 6 months after the last dose of Hu5F9-G4 or 6 months after the last dose of cetuximab, whichever occurs later.

Overdose

An overdose is a dose higher than that indicated in the protocol with or without an AE. Any overdose must be recorded in the trial drug section of the eCRF.

Abuse or Misuse

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

9.4. Expedited Reporting Requirements for Serious Adverse Events

9.4.1. Reporting Requirements for Fatal/Life Threatening SAEs Related to Investigational Products

Any life-threatening (i.e., imminent risk of death) or fatal AE assessed as related to the study drug(s) that occurs while on study drugs should be submitted to the Medical Monitor with written case details on an SAE Form within 24 hours of awareness, as described in Section 9.4.2.

Medical Monitor Contact Information for Sites:

Medical Monitor: Gani Chico, M.D.

Telephone No.: 650-352-4133

Alternate Telephone No.: 415-806-3145

Email: gchico@fortyseveninc.com

Alternate Medical Monitor Contact Information for Sites:

Medical Monitor: Mark Chao M.D., Ph.D.

Telephone No.: 650-776-7388

Alternate Telephone No.: 650-352-4141

Email: mchao@fortyseveninc.com

9.4.2. Reporting Requirements for All SAEs

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

The Sponsor or designee will report applicable serious adverse events and/or suspected unexpected serious adverse reactions (SUSARs) to regulatory authorities, Investigators/institutions, and central IRBs/IECs in compliance with reporting requirements according to local regulations and good clinical practice (GCP).

The Investigator is to notify the appropriate local IRB/IEC of serious adverse events occurring at the site and other applicable adverse event reports in accordance with local procedures and statutes.

9.5. Type and Duration of Follow-up of Patients after Adverse Events

The Investigator must follow all unresolved SAEs and study drug-related AEs until the events are resolved or stabilized, are determined to be irreversible by the Investigator, the patient initiates alternate therapy for their cancer, or the patient is lost to follow-up, whichever occurs first. Follow up will be conducted as described in Section 7.5. Resolution of AEs and SAEs (with dates) should be documented on the

Adverse Event eCRF and SAE Report Form (if applicable) and in the patient's medical record to facilitate SDV.

The Sponsor or its designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details (e.g., hospital discharge summary, consultant report, or autopsy report) deemed necessary to appropriately evaluate the SAE report. At any time, Investigators are to report SAEs that they assess to be related to one of the study drugs (Hu5F9-G4 and/or cetuximab received as part of this study).

10. MEASUREMENT OF EFFECT

10.1. Anti-cancer Effect

Patients will be assessed for response using the RECIST Version 1.1 Criteria (Eisenhauer 2009; Appendix D) and iRECIST (Seymour 2017, Appendix D).
The first response assessment will occur after 8 weeks of treatment. Subsequent response assessments will occur every 8 weeks. Tumor markers will be obtained, as appropriate, at baseline, and then every 4 to 8 weeks. Finally, response assessment will be obtained at the End of Treatment Visit, unless a prior radiographic assessment has been performed within the last 4 weeks or a prior response assessment documented progressive disease. Definitions of response parameters are provided in the subsections below.

10.2. RECIST Version 1.1

10.2.1. Evaluation of Lesions

Response and progression will be evaluated in this study using RECIST Version 1.1 Criteria, as detailed in Appendix D.

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

- Measurable tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: 10 mm by computed tomography (CT) scan (CT scan slice thickness no greater than 5 mm; Appendix D).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.
- 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.

Non-measurable lesions include lesions with longest diameter < 10 mm or pathological lymph nodes with < 15 mm short axis as well as truly non-measurable lesions. Lesions considered truly non-measurable include:

- Leptomeningeal disease
- Ascites
- Pleural or pericardial effusion
- Inflammatory breast disease
- Lymphangitic involvement of skin or lung
- Abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques

10.2.2. Assessment of Target Lesion Response

When more than 1 measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions. 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.

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.

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

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum measured while 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. However, because patients treated with immunotherapies may show pseudoprogression, patients with PD may continue investigational treatment through

RECIST Version 1.1-defined radiological progression of disease until disease progression is confirmed ≥ 4 weeks later (Nishino 2013; Hodi 2016) provided that all of the following apply: absence of clinical symptoms or signs indicating clinically significant disease progression; no decline in performance status; absence of rapid disease progression, or threat to vital organs or critical anatomical sites (e.g., CNS metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention; and no significant unacceptable or irreversible toxicities related to study treatment. If the confirmation scan demonstrates pseudoprogression and not PD, the patient may continue on treatment until disease progression is confirmed. The appearance of one or more new lesions is also considered progression according to RECIST Version 1.1 guidelines, however patients who meet the above criteria for non-clinically significant disease progression may also continue treatment until disease progression is confirmed (Hodi 2016).

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

10.2.3. Assessment of Non-target Lesions

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

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

PD: Unequivocal progression of existing non-target lesions. However, because patients treated with immunotherapies may show pseudoprogression, patients with PD may continue investigational treatment through RECIST Version 1.1-defined radiological progression of disease until disease progression is confirmed ≥ 4 weeks later (Nishino 2013, Hodi 2016), provided that all of the following apply: absence of clinical symptoms or signs indicating clinically significant disease progression; no decline in performance status; absence of rapid disease progression or threat to vital

organs or critical anatomical sites (e.g. CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention; and no significant unacceptable or irreversible toxicities related to study treatment. If the confirmation scan demonstrates pseudoprogression and not PD, patients may continue on treatment until disease progression is confirmed.

10.2.4. Assessment of Evaluable rather than Measurable Disease

Patients with evaluable but non-measurable response will be assessed with the diagnostic study used to establish evaluable disease at least every 8 weeks.
If serum tumor markers are being used to assess response, they are to be obtained every 4 to 8 weeks.

10.3. iRECIST

Detailed iRECIST Criteria are listed in Appendix D. More examples (Scenario A-F) of response evaluation by iRECIST are available in the supplementary appendix to iRECIST in Appendix D.

10.3.1. iRECIST Response Assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

10.3.1.1. Confirming Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression).

Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
    - Continued unequivocal progression in non-target disease with an increase in tumor burden
    - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.
- If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in Table 14, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

10.3.1.2. New Lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions) and recorded as New Lesions-Target

(NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Table 14 Time-point iResponse

			Time-point Response	
Target Lesions*	**Non-Target Lesions***	**New Lesions***	**No prior iUPD****	**Prior iUPD**; *****
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥ 5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: • further increase in SOM of at least 5 mm, otherwise remains iUPD

			Time-point Response	
Target Lesions*	**Non-Target Lesions***	**New Lesions***	**No prior iUPD****	**Prior iUPD**; *****
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • previously identified T lesion iUPD SOM ≥5 mm and / or • NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • previously identified T lesion iUPD ≥5 mm and / or • previously identified NT lesion iUPD (need not be unequivocal) and /or • size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on: • increase in size or number of new lesions previously identified

Abbreviations: CR = complete response; iCPD = immune confirmed progressive disease; iCR = immune complete response; iPR = immune partial response; iSD = immune stable disease; iUPD = immune unconfirmed progressive disease; NL = new lesion; NLT = new lesion - target; NLNT = new lesion - non-target; NT = non-target; PD = progressive disease; PR = partial response; SD = stable disease; SOM = sum of measures; T = target; TP = time point.

* Using RECIST 1.1 principles. If no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same.

** in any lesion category.

*** previously identified in assessment immediately prior to this TP.

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined in Table 15.

Table 15 iRECIST Best Overall Response (iBOR)

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

Abbreviations: CR = complete response; iBOR = immune best overall response; iCPD = immune confirmed progressive disease; iCR = immune complete response; iPR = immune partial response; iSD = immune stable disease; iUPD = immune unconfirmed progressive disease; NE = not evaluable that cycle; PD = progressive disease; PR = partial response; TPR = time-point response.

- Table assumes a randomized study where confirmation of CR or PR is not required.
- NE = not evaluable that cycle.
- •• For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

10.3.1.3. Response and Stable Disease Duration (RECIST 1.1 and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

10.3.1.4. Methods of Measurement

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. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the “merged lesion”.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

Chest X-ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans). Other specialized imaging or other techniques may also be appropriate for individual case. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used

providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

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

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

Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), 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 advised to differentiate between response or stable disease and progressive disease.

11. STATISTICAL CONSIDERATIONS

11.1. Analysis Sets

Enrolled Analysis Set (ENS) – includes all enrolled patients.

Typically, summary tables of disposition and protocol deviations will be performed on the ENS.

DLT Analysis Set - includes all enrolled patients who receive at least 1 dose of Hu5F9-G4 or cetuximab and either experience a DLT or complete at least 4 infusions of Hu5F9-G4 and 2 infusions of cetuximab.

Patients who withdraw before completing the 4-week DLT assessment period for reasons other than a DLT, or who do not fulfill either of the criteria above, will not be evaluable for dose review decisions and will be replaced in the cohort.

Efficacy Analysis Set (EAS) - includes all enrolled patients who received at least 1 dose of Hu5F9-G4.

The analysis of ORR, DOR, DCR, PFS, OS, and TTP will be performed on the Efficacy Analysis Set.

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

Safety analysis and demographics, etc. will be performed using the SAF.

Per Protocol Analysis Set (**PPS**) – includes includes all enrolled patients who do not have any important or major protocol deviations that might affect the efficacy outcomes.

A sensitivity analysis of ORR may be performed on the Per Protocol Analysis Set.

PK Analysis Set (**PAS**) - includes all enrolled patients who receive at least 1 dose of study drugs and have measurable concentrations of Hu5F9-G4 from PK blood samples.

11.2. Sample Size Determination

The total number of patients in this trial will include as many as 112 patients. This sample size includes the Phase 1b and Phase 2 parts of the study. In Phase 1b, a standard 3+3 dose escalation design will be used to explore the MTD of the investigational study drug combination in patients with solid tumors. An estimated 32 patients will be enrolled in Phase 1b, depending on dose escalation and expansion.

Phase 2 includes 2 arms, one comprising patients with KRAS mutant CRC and the other comprising patients with KRAS wild-type CRC, in which enrollment in one or both arms may be modified based on emerging data. A total of 88 patients (44 patients per arm) will be enrolled in Phase 2, assuming progression to Stage 2 for both arms. This sample size estimate was determined using a one-sided alpha level of 0.10 and a power of 0.80 based on a null hypothesis of 5% response rate compared to an alternative hypothesis of 15% for each cohort.

11.3. Statistical Methods

All analyses will be descriptive in nature. Descriptive statistics will be provided for all safety and efficacy endpoints.

All analyses will be conducted separately for patients in Phase 1b and Phase 2 parts of the study. However, safety analyses may be conducted for patients in both Phase 1b and Phase 2. In addition, efficacy analyses will be conducted separately for the two cohorts in Phase 2.

For continuous variables, the mean, standard deviation, median, and ranges will be provided. For categorical variables, the frequency and percentage in each category will be provided along with confidence intervals for primary and secondary efficacy endpoints. For time-to-event variables, the Kaplan-Meier (KM) estimates and corresponding two-sided 95% confidence intervals for the median and quartiles will be provided. The KM plot may also be provided. Details regarding the statistical

analysis to be conducted, including the handling of missing data and patient withdrawal, will be provided in the SAP.

11.3.1. Efficacy Analyses

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

11.3.1.1. Objective Response Rate

Objective response is defined as CR+PR determined by RECIST v 1.1 (primary efficacy) and iCR+iPR determined by iRECIST (secondary efficacy) separately. ORR is defined as the proportion of patients with objective response in the Efficacy Analysis Set.

A sensitivity analysis of ORR will be conducted on the Per Protocol Analysis Set if more than 10% of patients in the Efficacy Analysis Set are excluded from the Per Protocol Analysis Set.

11.3.1.2. Disease Control Rate

Disease control is defined as CR+PR+SD determined by RECIST v 1.1. DCR is defined as the proportion of patients with disease control in the Efficacy Analysis Set.

11.3.1.3. Duration of Response

DOR is measured from when the first (objective) response is met (i.e., CR or PR) until the first date of objectively documented progressive disease. Patients who do not have objectively progressive disease will be censored at their last documented progression-free date.

11.3.1.4. Progression-free Survival

PFS is measured from dose initiation until the first date of objectively documented progression disease or death. Patients who do not have objectively documented progression disease AND not died will be censored at their last documented progression-free date.

11.3.1.5. Overall Survival

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

11.3.1.6. Time to Progression

TTP is measured from dose initiation until the first date of objectively documented progressive disease. Patients who do not have objectively documented progressive disease will be censored at their last documented progression-free date.

Note: Term “objectively documented progressive disease” above refers to PD in the overall response evaluation form.

11.3.2. Pharmacokinetic/Pharmacodynamics Analyses

11.3.2.1. Pharmacokinetic Analyses

PK analysis will be conducted for Hu5F9-G4 and cetuximab using the PAS. Based on the distinct MOAs of Hu5F9-G4 and cetuximab, drug-drug PK interactions are not expected. Thus, samples for PK analysis for cetuximab will be biobanked and will be analyzed based on CTSC recommendation.

The PAS consists of all patients who have at least 1 blood sample that provides evaluable PK data. The PAS will be used for summaries of PK concentration data, and PK parameters. Individual patients may be removed from the estimation of particular PK parameters based on the number of available blood samples for them. These patients will be identified at the time of analysis.

The PK parameters to be assessed are presented in Table 16.

Table 16. Noncompartmental Pharmacokinetic Parameters

AUC_{last}	The AUC from time zero to the last measurable concentration sampling time (t_{last}) (mass × time × volume - 1)
AUC_{inf}	The AUC from time zero to infinity (mass × time × volume - 1)
AUC_{tau}	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount × time × volume - 1)
C_{max}	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass × volume - 1)
T_{max}	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
$T_{1/2}$	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL	The total body clearance of drug from the plasma (volume × time - 1)
V_z	The apparent volume of distribution during terminal phase (associated with λz) (volume)

PAS will be used in all PK data analysis and PK summary statistics, except for the dose-exposure analysis for Phase 1b.

Pharmacokinetic Variables

The following parameters will be determined by profile using non-compartmental method(s) for Hu5F9-G4:

- AUC_{inf}
- $AUC_{0\text{-}168h}$
- C_{max}
- T_{max}
- $T_{1/2}$
- CL
- V_z

Biofluid concentrations will be expressed in mass per volume units. All concentrations below the limit of quantitation or missing data will be reported as such in the concentration data listings. Concentrations below the limit of quantitation will be treated as zero in summary statistics.

Descriptive statistics of all PK parameters will include arithmetic and geometric mean, median, SD, CV, geometric CV, minimum and maximum. Zero

concentrations will not be included in the geometric mean calculation. Since T_{max} is generally evaluated by a nonparametric method, median values and ranges will be provided for this parameter.

Summary statistics will be presented for Hu5F9-G4 serum concentrations at each scheduled time point. Descriptive graphical plots of individual serum concentration-versus-time profiles and mean concentration-versus-time profiles will be generated.

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

11.3.2.2. Dose Proportionality

The analysis of dose proportionality will be conducted for the AUC and C_{max} of Hu5F9-G4 using a power model on log-transformed scale. The log-transformed PK parameters will each be regressed onto a fixed factor for log (dose). The 90% confidence interval (CI) of the slope for each PK parameter will be computed from the model and presented in a summary table.

11.3.2.3. Immunogenicity Analyses

The rate and magnitude of anti-Hu5F9-G4 antibody positivity will be evaluated for individual patients, for all patients in the Phase 1b and 2 parts of the trial, and for the pooled patient population. PPD

Immunogenicity analysis will also be performed for cetuximab. However, it is not expected that Hu5F9-G4 will impact the immunogenicity of cetuximab and vice versa.

Immunogenicity: Exposure and/or Adverse Event Relationship

The concentration-versus-adverse event/immunogenicity relationship will be explored graphically, tabulated and, if appropriate, evaluated by a mixed effects model in order to characterize a relationship between the changes from screening immunogenicity presence and serum concentration of Hu5F9-G4.

In addition, the potential correlation between immunogenicity and other endpoints (major safety, efficacy, and biomarker parameters) may be evaluated. This will be done in 2 steps. First, a descriptive analysis will be performed graphically between immunogenicity change from screening values and major safety, efficacy, and biomarker parameters (either as categories or continuous variables). Second, for any potential correlation identified, further investigation will be performed using a mechanism-based modeling approach, as appropriate.

11.3.2.4. Pharmacodynamic and Biomarker Analyses

PPD

11.3.3. Safety Analyses

The statistical analysis of safety will be conducted for patients in the SAF.
The statistical analysis will be descriptive, providing listings, graphical displays, frequencies, and percentages for discrete variables and/or the mean, standard deviation, median, and ranges for continuous variables. Safety variables to be examined include DLTs, treatment-emergent adverse events (TEAEs: AEs worsening or occurring during or after a patient's first exposure to study drugs), vital signs, physical examinations, laboratory, receptor occupancy, and antidrug antibody assessments. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 17.1 or later) and grouped by system organ class and preferred term.

Data will be presented by Phase 1b dose cohort and Phase 2 arm, where relevant, summarized across various dose cohorts. Data may be graphed, summarized, or listed depending on the amount of data to be reported. Where relevant, safety data will also be presented by the study day/study day interval corresponding to dose administrations within each dose cohort.

11.3.3.1. Adverse Events

For the safety Analysis Set, AEs that occurred during Screening, but before exposure to study drugs will be reported in the AE line listings and appropriately identified as non-TEAEs. Summary tables of TEAEs will be provided using the NCI CTCAE Version 4.03 to describe the type and severity of event. Peripheral smear assessments will be tabulated and reported separately. TEAEs will also be tabulated using Investigator assessment of the relationship to study drugs (related or not related). SAEs, including deaths, will be summarized and/or listed for each dose cohort and for all dose cohorts combined. TEAEs resulting in withdrawal from study drugs or further study participation will be tabulated and/or listed. DLTs will also be listed. Unless otherwise noted, the tabulation of AEs will be based on patient incidence rather than event incidence.

Adverse events and SAEs occurring during Screening will be reported separately for patients in the Screened-only Set with line listings and/or summary tables, along with relevant demographic data collected.

11.3.3.2. Analysis of Other Safety Endpoints

The analysis of other safety endpoints such as vital signs, peripheral smear assessments, and other laboratory assessments, will include listings, graphical displays, and descriptive statistics such as change from baseline and/or shift tables, where relevant. Details will be provided in the SAP.

11.4. Interim Analysis

An interim analysis would be conducted on the first 15 efficacy evaluable patients for each cohort in Phase 2. If median PFS is no more than 2 months and objective

response rate is less than 10%, then there would be no further enrollment into the cohort. CTSC would decide whether or not to further expand a cohort based on the totality of the efficacy as well as safety data.

12. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

12.1. Compliance Statement

This study will be conducted in accordance with the protocol and with US Food and Drug Administration (FDA) and the International Conference on Harmonisation (ICH) good clinical practice (GCP) guidelines, the Declaration of Helsinki, and any applicable local health authority and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) requirements.

To the extent applicable, all references to the FDA, Federal Food, Drug, and Cosmetic Act, Code of Federal Regulations (CFR), ICH, GCP, and the like shall be interpreted as also referring to any corresponding requirements of local regulatory agencies, regulations, and laws. If there is any discrepancy between FDA, ICH, and local requirements, the most stringent standard shall apply.

12.2. Investigator Responsibilities

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

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

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

The Investigator must inform the IRB/IEC of the progress of the clinical study and report any non-administrative changes made to the protocol; in any case, the

Investigator must provide an update to the IRB/IEC at least once a year or in accordance with IRB/IEC continuing approval requirements.

The Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs or other reporting forms will be included on the Forty Seven Inc. Delegation of Authority Form.

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

- a recognized expert in the therapeutic area.
- an Investigator who provided significant contributions to either the design or interpretation of the study.
- an Investigator contributing a high number of eligible patients.

12.3. Institutional Review Board or Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Forty Seven Inc. before recruitment of patients into the study and shipment of Hu5F9-G4.

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

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

12.4. Informed Consent and Human Subject Protection

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

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

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

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

12.5. Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained for documents submitted to Forty Seven Inc., including the following:

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the eCRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- For Serious Adverse Events reported to Forty Seven Inc., patients are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Forty Seven Inc. (e.g., signed informed consent forms) are to be kept in confidence by the Investigator, except as described below.

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

12.6. Urgent Safety Measures

The Sponsor or Investigator may take appropriate urgent safety measures to protect trial participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorization. The trial may continue with the urgent safety measures in place.

The Investigator must inform Forty Seven Inc. IMMEDIATELY if the study site initiates an urgent safety measure.

The notification must include all of the following:

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

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

12.7. Serious Breaches and Fraud

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

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

Investigators must notify Forty Seven Inc. immediately if any serious breach of GCP is suspected.

If there is any proof of fraud this must also be reported to Forty Seven Inc. All instances of confirmed clinical trial fraud occurring at sites in the UK will be treated

according to the procedure for dealing with a serious breach and must be reported to the MHRA within 7 days of the Sponsor becoming aware.

12.8. Study Monitoring

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

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

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

12.9. Audits and Inspections

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

12.10. Data Collection and Handling

The Investigator is responsible for complying with the requirements for all assessments and data collection (including patients not receiving protocol-required therapies), as stipulated in the protocol for each patient in the study. For patients

who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the SOA (Section 7.1), the Investigator may search publically available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

The Investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. Data collection will involve the use of the electronic data capture (EDC) system, to which only authorized personnel will have access. The Investigator agrees to maintain accurate electronic Case Report Form (eCRFs) (or paper Case Report Forms [CRFs]) and source documentation as part of the case histories. Forty Seven Inc. will supply the eCRF, which will be completed in English.

The Investigator or designee must enter all results collected during the clinical study into eCRFs. Guidelines for completion of eCRFs will be reviewed with study site personnel at the site initiation visits. Investigators are responsible for approval of the entered/corrected data. Detailed instructions may be found in the other study specific documents.

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

All data collected in the context of this study will be stored and evaluated according to regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to assure patient confidentiality in accordance with the legal and regulatory requirements applying to protected health information. Study records (e.g., copies of eCRFs, regulatory documents) will be retained at the study site, along with adequate source documentation. The study file

and all source data must be retained for the time period required by applicable regulatory requirements and will not be destroyed until written notification is given by the Sponsor or designee for destruction.

12.11. Maintenance of Source Documents and Record Retention

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

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

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

The Investigator must retain all essential documents for this clinical study until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of Hu5F9-G4. However, the Investigator may need to retain these documents for a longer period, if required by the applicable regulatory requirements or by an agreement with the Sponsor. A Sponsor representative will be responsible for informing the Investigator and study site regarding when they no longer need to retain these documents. Before destroying any records, the Investigator must notify the Sponsor and reach agreement on record destruction, or the Sponsor may request an additional retention period.

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

PPD

PPD

12.13. Financing and Insurance

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

12.14. Publication Policy

The Forty Seven Inc. publication policy is detailed in the Publication Charter.

13. REFERENCES

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14. APPENDICES

Appendix A: Cetuximab (Erbitux®) Prescribing Information

Available online:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125084s225lbl.pdf

Accessed 7 June 2016

Appendix B: National Cancer Institute Common Terminology Criteria for Adverse Events

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

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

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Accessed 06 August 2018

Appendix C: ECOG Performance Status

Eastern Cooperative Oncology Group Scale of Performance Status

Publication:

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

Karnofsky Performance Status

Publication:

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

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

Accessed 06 August 2018

Appendix D: RECIST Version 1.1 and iRECIST Guidelines

Publication:

Eisenhauer E, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (Version 1.1) Eur J Cancer 2009;45:228 – 247

http://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf

Accessed 06 August 2018

Seymour L, Bogaerts J, Perrone A, et al. iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar; 18(3): e143-e152.

http://recist.eortc.org/wp-content/uploads/2017/03/Manuscript_IRECIST_Lancet-Oncology_Seymour-et-al_revision_FINAL_clean_nov25.pdf

http://recist.eortc.org/wp-content/uploads/2017/03/Supplementary-material_iRECIST_Seymour-et-al_revision_FINAL_clean_nov25.pdf

Appendix E: Peripheral Smear Assessment

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

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

Abbreviations: RBCs = red blood cells.
Note: These guidelines are based on the Stanford Health Care Peripheral Blood Slide Review Manual, Version 3.0, 2015.

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

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