STATISTICAL ANALYSIS PLAN

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
STUDY DRUG:	Magrolimab (Hu5F9-G4)
VERSION NUMBER:	1.0
SPONSOR:	Forty Seven Inc
PLAN PREPARED BY:	PPD
DATE:	12 February 2020

Confidentiality Statement

Approval

Upon review of this document, including table, listing, and figure shells, the undersigned approves the Statistical Analysis Plan. The analysis methods and data presentation are acceptable.

Signature	Date
PPD PPD Forty Seven Inc.	Feb 14, 2020
PPD PPD Forty Seven Inc.	14 Feb 2020

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5F9	Hu5F9-G4, the experimental agent for this trial
ADA	antidrug antibodies
ATC	anatomical\therapeutic\chemical
CR	complete response
CRC	colorectal cancer
CTCAE	Common Terminology Criteria for Adverse Events
CTSC	Clinical Trial Steering Committee
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
eCRF	electronic case report form
iRECIST	modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) for cancer immunotherapeutic trials
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	preferred term
QW	every week
Q2W	every 2 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2DS	recommended Phase 2 dose and schedule
SOC	system organ class
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
TTP	time to progression
WHO	World Health Organization

1 INTRODUCTION

This document outlines the statistical methods and variable definitions to be implemented during the analyses of data in evaluation of efficacy, safety and PK/ADA of the clinical trial described in the Forty Seven Inc. protocol for Study 5F9004 entitled "A Phase 1b/2 Trial of Hu5F9-G4 in Combination with Cetuximab in Patients with Solid Tumor and Advanced Colorectal Cancer" Amendment 3, dated 28 Sep 2018. Analyses of biomarker data are out of scope of this SAP.

Analysis methods specified in this document take precedence over those described in the protocol should there be any difference.

1.1 Study Design

This trial is an open-label, multicenter Phase 1b/2 trial investigating the combination of magrolimab (Hu5F9-G4; hereafter referred to as 5F9) and cetuximab in patients with solid tumor and patients with advanced colorectal cancer (CRC). The study will be conducted in 2 parts:

- Dose escalation Phase 1b open to patients with solid tumors
- Phase 2 study 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, if one exists, and to identify a recommended Phase 2 dose and schedule (RP2DS) of 5F9 in combination with cetuximab. The dosing levels and schedules in each cohort are described in Table 1.

On all days on which both cetuximab and 5F9 are given, cetuximab will be given first. 5F9 will be given at least 1 hour after the cetuximab infusion is completed. Each cycle lasts 28 days.

Patients enrolled in the Phase 1b part of the study who have been on study for at least 8 weeks may have their dose escalated to a higher dose level if deemed safe at the discretion of the investigator and the Clinical Trial Steering Committee (CTSC).

The Phase 2 part of the study will incorporate a safety run-in by treating 9 patients with KRAS wild-type tumors at the RP2DS. If the tolerability of the regimen is confirmed in CRC patients after these 9 patients have completed the Dose-Limiting Toxicity (DLT) Assessment Period, 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. Enrollment will be held after 15 efficacy-evaluable patients for each cohort are enrolled. An interim analysis will be conducted. The CTSC will convene to review and approve proceeding with full accrual for Phase 2. The CTSC may also approve further enrollment and exploration of additional alternate Phase 2 doses that may enhance efficacy.

Table 1 Study Treatment Dose and Schedule for Phase 1b

Dose Cohort	Dose Levels in Cycle 1			5F9 Schedule in Cycle 2+[a]
	Day 1 (5F9 priming dose)	**Day 8** (5F9 maintenance dose + cetuximab loading dose)	**Day 15, 22** (maintenance dose)	
1	5F9 1 mg/kg	5F9 10 mg/kg + Cetuximab 300 mg/m2	5F9 10 mg/kg + Cetuximab 200 mg/m2	QW
2		5F9 10 mg/kg + Cetuximab 400 mg/m2	5F9 10 mg/kg + Cetuximab 250 mg/m2	
3		5F9 20 mg/kg + Cetuximab 400 mg/m2	5F9 20 mg/kg + Cetuximab 250 mg/m2	
4		5F9 30 mg/kg + Cetuximab 400 mg/m2	5F9 30 mg/kg + Cetuximab 250 mg/m2	
5[b]		5F9 45 mg/kg + Cetuximab 400 mg/m2	5F9 45 mg/kg + Cetuximab 250 mg/m2	C2: QW C3+: Q2W

Abbreviations: C = cycle; QW = every week; Q2W = every 2 weeks.
a Cetuximab is given on a weekly schedule.
b A loading dose of 5F9 at 45 mg/kg is given on Day 11.

The dose levels and schedules for 5F9 in each cohort are described in Table 2, in combination with cetuximab (a loading dose of 400 mg/m^2 followed by a maintenance dose of 250 mg/m^2 QW) in Phase 2.

Table 2 Study Treatment Dose and Schedule for Phase 2

Cohort	5F9 Dose Levels in Cycle 1			5F9 Schedule in Cycle 2+[a]
	Day 1 (5F9 priming dose)	**Day 8** (5F9 maintenance dose + cetuximab loading dose)	**Day 15, 22** (maintenance dose)	
KRASwt	5F9 1 mg/kg	5F9 30 mg/kg + Cetuximab 400 mg/m^2	5F9 30 mg/kg + Cetuximab 250 mg/m^2	Q2W
KRASm Cohort 1				
KRASm Cohort 2[b]		5F9 45 mg/kg + Cetuximab 400 mg/m^2	5F9 45 mg/kg + Cetuximab 250 mg/m^2	C2: QW C3+: Q2W

Abbreviations: C = cycle; KRASm = KRAS mutant; KRASwt = KRAS wild-type; QW = every week; Q2W = every 2 weeks.
a Cetuximab is given on a weekly schedule.
b A loading dose of 5F9 at 45 mg/kg is given on Day 11.

1.2 Study Objectives and Endpoints

PRIMARY	
OBJECTIVES	**ENDPOINTS**
• To investigate the safety and tolerability, and to determine the RP2DS for 5F9 in combination with cetuximab. • To evaluate objective response rate (ORR) of 5F9 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).	• 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 5F9 in combination with cetuximab. • To evaluate the immunogenicity of 5F9 in combination with cetuximab. • To evaluate efficacy of 5F9 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 5F9 in combination with cetuximab in patients with KRAS mutant and KRAS wild-type CRC according to iRECIST guidelines (Seymour 2017).	• 5F9 concentration versus time measurements of 5F9 in combination with cetuximab. • Antidrug antibodies to 5F9 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.

1.3 Sample Size Determination

Depending on dose escalation and expansion, an estimated number of 15 to 24 patients will be enrolled in Phase 1b, and 88 patients will be enrolled in Phase 2.

No formal hypothesis testing will be done. In Phase 2, it is planned to enroll an expansion cohort of 44 patients with KRAS mutant CRC and another expansion cohort of 44 patients with KRAS wild-type CRC. This sample size was determined using a one-sided alpha level of 0.10 and a power of 80% based on a null hypothesis of 5% response rate compared with an alternative hypothesis of 15% for each cohort.

2 ANALYSIS SETS

- **All Treated Patients**: includes all patients who receive at least 1 dose of any study drugs. Summary tables of disposition, demographics and other baseline characteristics, efficacy, and safety analyses will be performed on the All Treated Patients.
- **DLT Evaluable Analysis Set**: includes patients who received at least 1 dose of any study drugs during Phase 1b if the patient either experienced a DLT any time during the DLT Assessment Period (the first 4 weeks of treatment) or completed at least 4 infusions of 5F9 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. The same definition is applicable to the Phase 2 Safety Run-In to identify the first 9 DLT Evaluable Patients.
- **PK Analysis Set**: patients who receive any amount of magrolimab with at least one detectable post-treatment serum concentration of magrolimab are evaluable for PK analysis.
- **Immunogenicity Analysis Set**: patients with at least one reported ADA result will be included in the immunogenicity analysis set.

3 PATIENT INFORMATION

Disposition, demographics and other baseline characteristics, medical history, disease history, prior anticancer treatment, prior and concomitant medications, premedication, and efficacy will be presented for All Treated Patients.

3.1 Patient Disposition

The disposition table will include the following summaries: the number of patients treated, the number of patients who discontinued from the study treatment and of those from the study, reasons

for discontinuation, duration of treatment (months), and duration of follow up (months). The summaries will be provided for each dosing cohort (Phase 1b) or each expansion cohort (Phase 2), or at each maintenance dosing level.

3.2 Protocol Deviations

Patients with important protocol deviations will be identified and documented by the clinical team.

3.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics including age, sex, ethnicity, race, and weight as well as disease characteristics will be summarized.

3.4 Medical History

A listing will be provided for medical history.

3.5 Prior Cancer Treatments

The number and percentage of patients with each type of prior anticancer treatment (prior radiotherapy, prior cancer-related surgery, and prior cancer-related systemic therapy) will be summarized. The number of prior lines of cancer-related systemic therapies will also be summarized.

3.6 Prior and Concomitant Medications

Concomitant medication verbatim terms on electronic case report forms (eCRFs) will be coded to Anatomical/Therapeutic/Chemical (ATC) class and Preferred Names using the World Health Organization (WHO) Drug Dictionary Enhanced (version 01 Mar 2014).

Concomitant medications will be summarized by WHO ATC class and preferred name. The summarization includes all the concomitant medications taken any time while on study treatment (ie, from the date of first dose through the date of last dose of the study treatment), with exception of the premedication described in Section 6.1.2 of the protocol, which will be summarized separately (see the next subsection). Each patient will be counted once for each preferred name, and each ATC class.

Prior medication is defined as any medication with a start date prior to the date of first dose, regardless of when the stop date is. A listing of prior medication together with concomitant medications will be provided.

3.7 Premedication

Premedication is required before administration of the first cetuximab dose and before the first 2 doses of 5F9 (inclusive of the priming dose). The number and percentage of patients who received the following premedication will be summarized:

- Oral acetaminophen 650 to 1000 mg and oral or intravenous diphenhydramine 25 mg, or comparable regimen on the date of but prior to the first 2 doses of 5F9 (inclusive of the priming dose)
- H1 antagonist (eg, 50 mg of diphenhydramine) intravenously and other agents (ie, glucocorticoids, etc.) on the date of but prior to the first cetuximab dose

3.8 Subsequent Lines of Anticancer Therapy

Subsequent therapies received after the last dose of study treatment will be summarized by WHO ATC class and preferred names. Each patient will be counted once for each preferred name, and each ATC class.

4 EFFICACY ANALYSIS

Confirmed best response based on RECIST v1.1 will be summarized for All Treated Patients with CRC by cohort for KRAS wild-type and KRAS mutant patients separately. ORR will be calculated based on All Treated Patients with measurable disease at baseline.

PFS is defined as the duration of time from dose initiation to the first date of objectively documented disease progression per RECIST v1.1 or death. Patients who do not have objectively documented disease progression and did not die will be censored at their last tumor assessment date.

OS is defined as the duration of time from dose initiation to the date of death due to any cause. Patients who did not die will be censored at their last known alive date.

Both PFS and OS will be summarized using Kaplan-Meier methods and summary statistics will include their 95% confidence intervals for All Treated Patients with CRC by cohort for KRAS wild-type and KRAS mutant patients separately.

5 PHARMACOKINETIC ANALYSES

5.1 Pharmacokinetic Analysis

The PK Analysis Set will be used in the analysis of PK data. Descriptive statistics of magrolimab concentration data will be provided. Individual and mean serum concentration-time profiles of

magrolimab per cohort for each study part will be generated. Non-compartmental PK data analysis may be performed when data allows and PK parameters such as C_{max} and AUC will be reported when appropriate. Additional parameters may be calculated as deemed appropriate.

5.2 Immunogenicity Analysis

The prevalence, incidence, and titer of anti-5F9 antibodies (antidrug antibodies or ADA) will be evaluated for individual patients and will be listed and summarized for each dose cohort for each study part and for the pooled patient population. ADA incidence, prevalence, and transience versus persistence will be summarized. PPD

6 SAFETY ANALYSIS

All safety analyses will be performed by the actual 5F9 maintenance dose level based on the All Treated Patients.

6.1 Extent of Exposure

Exposure to study treatment will be summarized in each cohort for the All Treated Patients. Descriptive statistics will be provided for the following data for each study drugs (5F9, Cetuximab): treatment duration; total number of study drug infusions; cumulative dose administered; the number of missed/delayed doses, including those due to AE; the number of dose reductions; the number of dose interruptions, including those due to AE; and median time to first missed, delayed, or interrupted dose due to AE or dose reduction.

6.2 Adverse Events

Treatment-emergent adverse events (TEAE) will be summarized in each cohort. Summaries will be restricted to TEAEs are defined as those AEs that worsened or occurred during or after a patient's first dose of any study drug and those existing AEs that worsened during the study and within 30 days after the last administration of any study drug or initiation of new anticancer therapy, whichever occurred first. If it cannot be determined whether the AE is treatment-emergent due to a partial onset date then the AE will be included in the TEAE summary. Verbatim terms on eCRFs will be coded to system organ class (SOCs) and preferred terms (PTs) using the Medical Dictionary for Regulatory Activities Version 19.0. NCI-CTCAE Version 4.03 will be used to summarize type and severity of the events, except for hemagglutination and microangiopathy events, which will be assessed per the protocol specified (Section 6.1.5.2.1) severity scoring.

The following summaries will be presented:

- Overview of AEs.
- Patient incidence of TEAEs by PT.
- Patient incidence of treatment-related adverse events (TRAEs) by PT.
- Patient incidence of TEAEs by SOC and PT, showing each grade and overall.
- Patient incidence of serious TEAEs by SOC and PT, showing each grade and overall.
- Patient incidence of TRAEs by SOC and PT.
- Patient incidence of Grade 3 or higher TEAEs by SOC and PT.
- Patient incidence of Grade 3 or higher TRAEs by SOC and PT.
- Patient incidence of TEAEs as part of an infusion reaction identified by the investigator by SOC and PT, showing each grade and overall
- Patient incidence of TEAEs leading to study drug discontinuation by SOC, PT, and worst grade.
- Patient incidence of TEAEs leading to dose interruption by SOC and PT.
- Patient incidence of TEAEs leading to dose delay/reduction by SOC and PT.

A further summary of the number of patients experiencing DLTs and the average number of infusions in these patients will be tabulated.

Listings of all AEs including TEAEs, TEAEs related to either 5F9 or cetuximab, Grade 3 or higher TEAEs, TEAEs that the investigator identified as part of an infusion reaction, serious TEAEs, TEAEs leading to study discontinuation, TEAEs leading to interruption or dose delay/reduction, DLT events, and deaths will be provided.

6.3 Deaths

All deaths and causes of death on study will be summarized and listed.

6.4 Clinical Laboratory Evaluation

Selected laboratory parameters (serum chemistry, hematology, prothrombin time/international normalized ratio, and activated partial thromboplastin time) will be summarized.

Laboratory parameters will be graded according to CTCAE Version 4.03. The worst postbaseline CTCAE grade will be summarized using a shift table to assess changes from baseline for the key variables. Summaries of treatment-emergent laboratory toxicities of serum chemistry and hematology will be tabulated by counts and percentages.

Laboratory data listings will include CTCAE grades and flags for those values outside the reference ranges. Urinalysis examination will only be presented in a data listing.

6.5 Vital Signs

Vital sign measurement results will only be provided in a data listing.

6.6 Physical Examination

Physical examination results will only be provided in a data listing.

6.7 Electrocardiogram

Electrocardiogram results will only be provided in a data listing.

6.8 Peripheral Blood Smear

Peripheral blood smear parameters will be summarized using frequency counts with percentages at each time point.

6.9 Visual Acuity and Retinal Imaging

Visual acuity and retinal imaging data will only be provided in a data listing.

7 CHANGES TO PROTOCOL-SPECIFIED ANALYSES

The following modifications have been made to the analyses specified in Protocol Amendment 3:

- The definition of treatment-emergent period was updated to specify an end date for each patient's reporting period to be within 30 days after the last administration of study drug or initiation of new anticancer therapy, whichever occurred first.
- Endpoint TTP will not be summarized.
- The tumor assessment based on iRECIST will not be reported.
- All enrolled patients received at least 1 dose of 5F9. Enrolled Analysis Set, Efficacy Analysis Set, and Safety Analysis Set are consolidated into All Treated Patients for all efficacy and safety analyses. Per-Protocol Analysis Set is not defined any more.

8 REFERENCES

Eisenhauer EA, 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.

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