CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1b Trial of Hu5F9-G4 in Combination with Avelumab in Solid Tumor Patients and Checkpoint-Inhibitor-Naïve Ovarian Cancer Patients Who Progress within 6 Months of Prior Platinum Chemotherapy
Protocol Number:	5F9006
Investigational Medicinal Product:	Hu5F9-G4 in combination with avelumab
Indication:	Ovarian cancer
Development Phase:	1b
US IND Number:	136624
EudraCT Number:	NA
Sponsor:	Forty Seven Inc. 1490 O'Brien Drive, Suite A Menlo Park, CA 94025 USA Telephone: PPD Fax: PPD
Medical Monitor:	PPD Forty Seven Inc. Telephone: PPD Email: PPD
Study Monitor:	PPD Clinical Operations Clinical Operations, Forty Seven Inc. Telephone: PPD Email: PPD
Amendment 3 Date:	22 December 2018
Amendment 2 Date:	14 August 2018
Amendment 1 Date:	30 April 2018
Original Protocol Date:	5 February 2018

Compliance Statement:

This study will be conducted in accordance with this protocol, 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

4 Jan 2019

PPD

Date

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 reason for amending the 5F9006 protocol is to remove the requirement that patients have received liposomal doxorubicin therapy prior to entering Part 2 this study.

The following substantial change has been made to Section 4.1 (Inclusion Criteria):

- Inclusion Criterion 1 for Study Part 2 has been modified to remove the requirement that patients have received prior liposomal doxorubicin therapy and specify that patients must have documented PD, as determined by Gynecologic Cancer InterGroup (GCIG) Criteria (Rustin 2011), within 1-6 months after the last day they received the last platinum containing chemotherapy.
  Rationale: To simplify the enrollment of a homogeneous group of patients with platinum resistant ovarian cancer and allow more patients to potentially participate in the study by removing the requirement for prior doxil therapy.

The following additional changes have been made to the protocol in this amendment:

- Specified that T3 (Total) is to be measured (Table 7-1 and Table 7-2) and added T3 (Total) and T4 (Free) to the TSH assessment in Table 7-3 and the Analyte Listing (Table 7-5).
  Rationale: To accurately specify the tests being performed to measure thyroid function.
- Reorganization and consolidation of safety language (Section 9, Assessment of Safety, and Table 7-3, Footnote “e”).
  Rationale: To provide more concise content and align language across Forty Seven Inc. protocols.

Editorial changes and updates to style and formatting have been made to improve clarity and consistency throughout the document. Changes made 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 avelumab

Protocol Number: 5F9006

Study Title: A Phase 1b Trial of Hu5F9-G4 in Combination with Avelumab in Solid Tumor Patients and Checkpoint-Inhibitor-Naïve Ovarian Cancer Patients Who Progress within 6 Months of Prior Platinum Chemotherapy

Scientific Rationale and Background

Ovarian cancer is the most frequent cause of gynecologic cancer deaths in the United States. Standard of care for this disease in the frontline and platinum-sensitive recurrent setting is platinum-based chemotherapy with or without antiangiogenic agents. More recently, targeted agents such as poly adenosine-diphosphate ribose polymerase (PARP) inhibitors have been approved by the Food and Drug Administration for women with ovarian cancer (BRCA) mutations and/or alterations in the homologous recombination pathway. Experience with newer immunotherapies in this disease, such as the checkpoint inhibitors, has not yet matured to impact clinical outcomes. In women with recurrent ovarian cancer, the platinum-free interval (PFI), defined as the interval between the last platinum dose and the date of relapse (Rustin 2011), is strongly correlated with the likelihood of response to subsequent chemotherapy. Patients who initially respond to systemic therapy with a PFI greater than 1 month, but less than 6 months, have been historically referred to as platinum-resistant, and these patients have limited treatment options (Davis 2014). Thus, the development of effective cancer treatments for this patient population would address a substantial unmet medical need.

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 signal regulatory protein alpha (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 (Liu 2015b). 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.

Patients with advanced ovarian cancer who have relapsed or are resistant to platinum-based chemotherapy have limited options for effective treatment and an overall poor prognosis (Davis 2014). Consequently, a well-tolerated immunotherapy combination that can induce anti-tumor responses and prolong progression-free survival (PFS) and overall survival (OS) would be an important therapeutic advance in the management of disease in these patients. Preliminary clinical data from Hu5F9-G4 monotherapy in patients with solid tumors suggest that blockade of CD47 may induce objective responses in heavily pretreated patients with ovarian cancer. Furthermore, preclinical studies and our understanding of the mechanism of Hu5F9-G4 action suggest that targeting CD47 may generate substantial synergistic anti-tumor activity when combined with programmed cell death-ligand 1 (PD-L1) checkpoint inhibitors. Thus, the scientific rationale for exploring the efficacy of this combination in this setting is strong.

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**
Safety Run-in Cohort: To investigate the safety and tolerability of Hu5F9-G4 in combination with avelumab in patients with advanced solid tumors **Ovarian Cancer Expansion Cohort**: To confirm the safety and tolerability of this combination and evaluate the anti-tumor activity based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer 2009) in patients with checkpoint inhibitor-naïve ovarian cancer, fallopian tube cancer, and primary peritoneal carcinoma who have previously progressed within 1-6 months of receiving platinum chemotherapy	AEs and DLTs graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 (Appendix C) or customized AE severity grading for hemagglutination and microangiopathy, as defined in Protocol Section 6.5.1.3 (Safety Management Guidelines) Objective response as defined by the Investigator according to RECIST v1.1 (Eisenhauer 2009)
SECONDARY	
OBJECTIVES	**ENDPOINTS**
Safety Run-in Cohort: To determine a recommended dose of Hu5F9-G4 + avelumab in patients with solid tumors To examine the pharmacokinetic (PK) profile of Hu5F9-G4 in combination with avelumab To evaluate the immunogenicity of Hu5F9-G4 in combination with avelumab	Recommended Phase 2 dose and schedule (RP2DS) of Hu5F9-G4 in combination with avelumab Serum concentrations of Hu5F9-G4 collected at selected time points Anti-drug antibodies (ADA) to Hu5F9-G4
Ovarian Cancer Expansion Cohort: To evaluate the anti-tumor activity of Hu5F9-G4 in combination with avelumab in all patients using the Immune Response Evaluation Criteria in Solid Tumors (irRECIST; Bohnsack 2014) and, where applicable, the Gynecologic Cancer Intergroup (GCIG) response criteria (Rustin 2011) To assess additional efficacy endpoints including duration of response (DOR), time to tumor progression (TTP), progression-free survival (PFS), and overall survival (OS) To evaluate the impact of Hu5F9-G4 in combination with avelumab on the myeloid cell populations in the tumor	**Ovarian Cancer Expansion Cohort**: Objective response, as defined by the Investigator according to irRECIST (Bohnsack 2014) and GCIG response criteria (Rustin 2011) For patients who respond, DOR will be evaluated. For all patients, efficacy endpoints will include TTP, PFS, and OS. Immunohistochemical staining of myeloid cells in formalin-fixed, paraffin-embedded tissues

microenvironment, as assessed in sequential tumor biopsies in patients with platinum-resistant ovarian cancer	
CCI [redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Overall Study Design:

This is an open label, multicenter, Phase 1b trial investigating the combination of Hu5F9-G4 and avelumab in patients with solid tumors and checkpoint inhibitor-naïve ovarian cancer who progressed within 1-6 months of receiving platinum-containing chemotherapy. Checkpoint inhibitor-naïve patients are defined as those patients who have not been previously treated with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab, tremelimumab, or any other antibody or drug specifically targeting T-cell co-regulatory proteins).

CCI [redacted] in Part 2, mandatory pretreatment and during-treatment biopsies will be collected as described in Protocol Section 7.3.11.

The study will be conducted in 2 parts: Part 1 (Dose Evaluation/Safety Run-in) and Part 2 (Expansion in Ovarian Cancer), as follows:

Part 1 - Dose Evaluation/Safety Run-in

Patients with solid tumors will be treated at the starting dose with Hu5F9-G4 + avelumab to examine the safety and pharmacokinetics (PK) of this study drug

combination. The Safety Run-in Cohort will begin by treating 6 patients, up to a total of 12 patients evaluable for dose-limiting toxicity (DLT).

The dose levels and schedules for both study drugs are described in Synopsis Table 2. Dose evaluation decisions will be made by the Clinical Trial Steering Committee (CTSC), and DLTs for the combination regimen will be monitored from administration of the priming dose on Day 1 to the end of Cycle 1 (Day 35). The first patient in each dose level cohort will be treated for 14 days prior to enrolling additional patients. After the first 6 patients evaluable for DLT assessment have safely completed the Cycle 1 DLT evaluation period, and if no more than 1 DLT occurs, the cohort will be deemed to be safe by the CTSC (Protocol Section 11.3) (Synopsis Table 2). The recommended dose for patients in the Expansion Cohort must have a DLT rate less than 33% in at least 6 evaluable patients, and the final dose selection for Part 2 will be made by the CTSC after all available clinical, CCI [redacted] and PK data are reviewed. Up to an additional 6 evaluable patients may be enrolled in any cohort to further evaluate safety and PK.

The first cycle will be 5 weeks in duration; subsequent cycles will last 4 weeks. Initial tumor response assessments will be performed at Cycle 3 and then after every 8 weeks of treatment (every 2 cycles). CCI [redacted]

Dose-Limiting Toxicity Definition

A DLT is defined as any Grade 3 or greater adverse event (AE) that is assessed as related to at least 1 study drug that occurs during the 5-week DLT Assessment Period, defined as the first 5 weeks of treatment for each patient. Additionally, any treatment-emergent adverse event (TEAE) that is, in the opinion of the CTSC, of potential clinical significance such that further dosing would expose patients to unacceptable risk, will be considered a DLT. Exceptions to the DLT definition are outlined in Protocol Section 3.2.1.2. DLT assessment is outlined in Protocol Section 3.2.1.

Synopsis Table 2: Part 1 Hu5F9-G4 and Avelumab Dose Levels and Schedule

Dose Cohort	Drug/Dose (Intravenous)	Dose Schedule		
		Cycle 1 (35 days)	Cycle 2 (28 days)	Cycle 3+ (28 days)
1	Hu5F9-G4 — 1 mg/kg (priming dose) *Over 3 hours (± 30 minutes)* *Infusion should begin at least 1 hour after completion of the avelumab infusion (on days when both are administered)*	Day 1	—	—
	Hu5F9-G4 — 30 mg/kg *Over 2 hours (± 30 minutes)* *Infusion should begin at least 1 hour after completion of the avelumab infusion (on days when both are administered)*	Days 8, 15, 22, 29	Days 1 and 15	Days 1 and 15
	Avelumab — 800 mg Q2W *Over 1 hour (-10 to +20 minutes)*	Days 8 and 22	Days 1 and 15	Days 1 and 15
2	Hu5F9-G4 — 1 mg/kg (priming dose) Over 3 hours (± 30 minutes) *Infusion should begin at least 1 hour after completion of the avelumab infusion (on days when both are administered)*	Day 1	—	—
	Hu5F9-G4 — 45 mg/kg Over 2 hours (± 30 minutes) *Infusion should begin at least 1 hour after completion of the avelumab infusion (on days when both are administered)*	Days 8, 11, 15, 22, 29	Days 1, 8, 15, 22	Days 1 and 15
	Avelumab — 800 mg Q2W Over 1 hour (-10 to +20 minutes)	Days 8 and 22	Days 1 and 15	Days 1 and 15
The following lower dose cohort may be used if ≥2 of 6 patients in Dose Level 1 experience DLTs:				
-1	Hu5F9-G4 — 1 mg/kg (priming dose) Over 3 hours (± 30 minutes) *Infusion should begin at least 1 hour after completion of the avelumab infusion (on days when both are administered)*	Day 1	—	—

Dose Cohort	Drug/Dose (Intravenous)	Dose Schedule		
		Cycle 1 (35 days)	Cycle 2 (28 days)	Cycle 3+ (28 days)
	Hu5F9-G4 — 20 mg/kg [a] Over 2 hours (± 30 minutes) *Infusion should begin at least 1 hour after completion of the avelumab infusion (on days when both are administered)*	Days 8, 15, 22, 29	Days 1 and 15	Days 1 and 15
	Avelumab — 800 mg Q2W Over 1 hour (-10 to +20 minutes)	Days 8 and 22	Days 1 and 15	Days 1 and 15
The following lower dose cohort may be used if ≥2 of 6 patients in Dose Level 2 experience DLTs:				
-2	Hu5F9-G4 — 1 mg/kg (priming dose) Over 3 hours (± 30 minutes) *Infusion should begin at least 1 hour after completion of the avelumab infusion (on days when both are administered)*	Day 1	—	—
	Hu5F9-G4 — 30 mg/kg [a] Over 2 hours (± 30 minutes) *Infusion should begin at least 1 hour after completion of the avelumab infusion (on days when both are administered)*	Days 8, 11, 15, 22, 29	Days 1, 8, 15, 22	Days 1 and 15
	Avelumab — 800 mg Q2W Over 1 hour (-10 to +20 minutes)	Days 8 and 22	Days 1 and 15	Days 1 and 15

Abbreviations: DLT = dose-limiting toxicity; Q2W = once every 2 weeks.
a. If additional dose reductions are required but the patient is deemed to be benefitting from treatment, the dose of Hu5F9-G4 may be reduced by an additional 50%.

Part 2 - Expansion in Ovarian Cancer:

Checkpoint inhibitor-naïve ovarian cancer patients will be treated with Hu5F9-G4 + avelumab to evaluate the safety, efficacy, CCI [redacted] effects of this study drug combination.

Once the Part 1 Safety Run-in Cohort of the trial is completed and the recommended expansion dose(s) is determined, the CTSC will open Part 2 of the study. Part 2 of the study will treat up to 20 patients with ovarian cancer at the recommended

dose(s) to confirm safety, PK, CCI [redacted] and to document preliminary efficacy in this population.

In Part 2, patients may be enrolled simultaneously without an observation period after the first patient starts treatment. Based on review of ongoing dosing data, the CTSC may recommend testing of multiple doses in Phase 2 and each dose level tested will enroll a total of 20 patients. In Part 2, mandatory tumor biopsies will be collected, where medically feasible, from all patients during the Screening Period prior to first dose and at Cycle 3, Day 1 (± 2 weeks). CCI [redacted] Efficacy will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST v1.1; primary endpoint; Eisenhauer 2009) and Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST; secondary endpoint; Bohnsack 2014). Study treatment may be continued until an unacceptable drug-related toxicity occurs or until disease progression according to irRECIST.

Clinical Trial Steering Committee (CTSC)

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 Part 2 CCI [redacted]. The CTSC will meet at a minimum at the completion of the DLT period for each cohort in the Safety Run-in part 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

Patients may continue treatment unless they develop unacceptable toxicities that cannot be clinically managed by dose or schedule modifications as outlined in Protocol Section 6.4, or if they have confirmed progressive disease (PD) according to irRECIST, as described in Protocol Section 10.1. Hu5F9-G4 and avelumab combination treatment may continue past the initial determination of disease progression according to irRECIST as long as the following criteria are met:

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

The decision to continue treatment should be discussed with the Medical Monitor and documented in the trial records.

Overview of Assessments

Assessments will be performed according to the schedules provided in Protocol Section 7 (Table 7-1, Table 7-2, Table 7-3, and Table 7-4).

Safety assessments include vital signs, physical exam, electrocardiograms, ECOG performance status score, pregnancy testing (for female patients), AEs, laboratory tests (hematology, serum chemistries, urinalysis, and coagulation), monitoring of concomitant medications, and incidence of anti-drug (ADA) antibodies.

Appropriate cancer staging assessments should be performed. Response assessments will be by imaging to be conducted according to RECIST v1.1 and irRECIST as described in Protocol Section 10.1. The same imaging modality used at Screening should be used throughout the study whenever possible.

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 was performed within the past 4 weeks or a prior response assessment showed documented confirmed PD.

Tumor markers should be obtained at Screening (Section 7.3.11). If applicable, they should be obtained on Day 1 of Cycles 2, 3, and 4. From Cycle 5 and onward, they may be obtained every 2 cycles.

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

Planned Number of Patients

The Safety Run-in Cohort (Part 1) will begin by treating 6 patients and will enroll up to 18 patients evaluable for DLT.

The Ovarian Cancer Expansion Cohort (Part 2) will treat up to 20 patients with ovarian cancer at the recommended dose to confirm safety, PK, CCI and to document preliminary efficacy in this population. Each dose level tested in Phase 2 will enroll a total of 20 patients.

Inclusion Criteria (All Patients)

1. Meets the criteria for the appropriate cohort:
    - Part 1 Safety Run-in Cohort: Pathologically confirmed advanced solid tumors for which no further conventional therapy is suitable for the patient and for which there is no curative therapy available. Prior checkpoint inhibitor treatment therapy is permitted.
    - Part 2 Ovarian Cancer Expansion Cohort: Histologically or cytologically confirmed, epithelial ovarian, fallopian tube, or peritoneal cancer patients who are checkpoint inhibitor-naïve. All histological subtypes of ovarian epithelial tumors are allowed. Patients must have had, at any point, documented PD as determined by Gynecologic Cancer InterGroup (GCIG) criteria (Rustin 2011) within 1-6 months after the last day of receiving the last platinum-containing chemotherapy. Patients must have received at least 1 prior line of a platinum-based chemotherapy regimen to be eligible. Patients may have received any additional number of prior systemic therapies for metastatic disease including PARP inhibitors.
2. Part 2 Ovarian Cancer Expansion Cohort: Disease must be measurable or assessable for response according to RECIST v1.1 (primary endpoint) and irRECIST (secondary endpoint).
3. Age ≥18 years.
4. ECOG Performance Status 0 to 2 (Appendix D).

5. Laboratory measurements, blood counts:
    - Hemoglobin ≥9.5 g/dL (red blood cell [RBC] transfusions are permitted during the Screening Period and prior to enrollment to meet the hemoglobin inclusion criterion.)
    - Absolute neutrophil count (ANC) ≥1.5 × 10^9/L.
    - Platelets ≥100 × 10^9/L.
6. Laboratory measurements, hepatic function:
    - Aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN), or ≤5 × ULN for patients with intrahepatic liver metastases.
    - Bilirubin ≤1.5 × 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. For patients in Part 1 CCI [redacted] a formalin-fixed paraffin-embedded (FFPE) block containing tumor tissue not older than 6 months from the time of screening or a minimum of 10 (preferably 25) unstained tumor slides (cut within 1 week) suitable for PD-L1 expression assessment will be collected. The tissue should be collected from a non-irradiated area and there should be at least 1 measurable lesion remaining for tumor response assessment.
9. Negative urine or serum pregnancy test within 30 days before enrollment and within 72 hours before the first administration of study drug for female patients of childbearing potential.
10. Female patients of childbearing potential must be willing to use 1 highly effective method of contraception during the study and continue for 4 months

after the last dose of Hu5F9-G4 and 1 month after the last dose of avelumab (Protocol Section 4.6.1).

11. Male patients who are sexually active with a woman of childbearing potential and who have not had vasectomies must be willing to use a highly effective barrier method of contraception during the study and for 4 months after the last dose of Hu5F9-G4 and 1 month after the last dose of avelumab (Protocol Section 4.6.2).
12. Patient has provided informed consent.
13. Must be willing and able to comply with the clinic visits and procedures outlined in the study protocol.
14. For Part 2 (Ovarian Cancer Expansion Cohort) only: Willing to consent to 1 mandatory pre-treatment and 1 during-treatment tumor biopsy unless not medically feasible as determined 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 symptomatic or untreated central nervous system (CNS) metastases. (Patients with stable, asymptomatic, treated CNS lesions, who are off of corticosteroids and radiation therapy for at least 3 weeks are permitted.)
2. Prior or concurrent 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.
   The following are not criteria for exclusion:
   - Localized non-CNS radiotherapy (>14 days before enrollment)
   - Previous hormonal therapy with luteinizing-hormone releasing hormone (LHRH) agonists for prostate cancer

- Low dose steroids (oral prednisone or equivalent ≤10 mg per day)
- Treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors

3. For Part 2 Ovarian Cancer Expansion Cohort only: Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab, tremelimumab, or any other antibody or drug specifically targeting T-cell co-regulatory proteins).
4. Prior treatment with CD47 or SIRPα targeting agents.
5. Known active or chronic hepatitis B or C infection or human immunodeficiency virus (HIV).
6. RBC transfusion dependence, defined as requiring more than 2 units of RBCs transfused during the 4-week period prior to Screening. RBC transfusions are permitted during the Screening Period and prior to enrollment to meet the hemoglobin inclusion criteria.
7. Prior organ transplantation, including allogeneic stem-cell transplantation, requiring immunosuppression.
8. Prior hemolytic anemia or Evans Syndrome in the last 3 months.
9. Hypersensitivity to the active substance or to any of the other excipients of Hu5F9-G4 or avelumab, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.03, Grade ≥3; Appendix C).
10. Significant medical diseases or conditions that would substantially worsen 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, significant acute or chronic infections, severely immunocompromised state, and congestive heart failure (New York Heart Association [NYHA] Class II-IV).
11. Known history of inflammatory colitis, inflammatory bowel disease, pneumonitis, or pulmonary fibrosis.
12. History of uncontrolled intercurrent illness including but not limited to:

- Hypertension uncontrolled by standard therapies (not stabilized to 150/90 mmHg or lower)
- Uncontrolled active infection
- Uncontrolled diabetes (e.g., hemoglobin A1c ≥8%)
- Uncontrolled asthma

13. Radiotherapy within 14 days prior to enrollment.
14. For Part 2 Expansion Cohort only: Previous malignant disease (other than the tumor disease for this trial and with the exception of adequately treated non-melanoma skin cancers, and carcinoma in situ of skin, bladder, cervix, colon/rectum, or breast) unless in a stable remission for at least 2 years prior to study entry.
15. History of psychiatric illness or substance abuse likely to interfere with ability to comply with protocol requirements or give informed consent.
16. Patient or designees are or become incapable of providing legal informed consent.
17. Current use of the following medications at the time of enrollment:
    - Immunotherapy or immunosuppressive drugs (e.g., chemotherapy or systemic corticosteroids) EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent; c. steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
    - Growth factors (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor) EXCEPT for erythropoietin and darbepoetin alpha.
    - Herbal remedies with immunostimulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (e.g., hypericin).
18. Administration of a live vaccine within 28 days prior to enrollment.

19. Pregnancy or active breast feeding.

20. Active autoimmune disease or treatment with systemic immunosuppression for organ transplantation.

    The following are not criteria for exclusion:

    - Type I diabetes mellitus
    - Vitiligo
    - Mild-to-moderate psoriasis
    - Clinically stable hypo- or hyperthyroid disease not requiring immunosuppressive treatment

21. Positive IgG component of the direct antiglobulin test (DAT).

Test Product, Dose, and Mode of Administration

Hu5F9-G4 is 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. Hu5F9-G4 is a humanized monoclonal antibody against CD47 which is administered intravenously (IV).

Part 1 Dose: The precise starting dose for Hu5F9-G4 will be a priming dose of 1 mg/kg in Week 1 followed by 30 mg/kg weekly for 4 doses. Starting in Cycle 2, 30 mg/kg of Hu5F9-G4 will be given every 2 weeks. This Hu5F9-G4 dose will be combined with the full single-agent dose of 800 mg of avelumab given once every 2 weeks (Synopsis Table 2). Other doses and schedules may be tested as described above in Part 1: Dose Evaluation/Safety Run-in.

Part 2 Dose: Once the Part 1 Safety Run-in Cohort of the trial is completed and the recommended expansion dose(s) is determined, the CTSC will open Part 2 of the study. Part 2 of the study will treat up to 20 patients with ovarian cancer at the recommended dose(s) to confirm safety, PK, CCI [redacted] and to document preliminary efficacy in this population. Each dose level tested in Phase 2 will enroll 20 patients.

Combination Therapy, Dose, and Mode of Administration

Avelumab (BAVENCIO®) is a programmed death ligand-1 (PD-L1) blocking antibody. Avelumab is a human IgG1 lambda monoclonal antibody that has a molecular weight of approximately 147 kDa.

Part 1 Dose: Avelumab will be administered IV at a fixed dose of 800 mg over 1 hour (-10 to +20 minutes) (Synopsis Table 2). Because of the different cycle lengths (due to the priming dose of Hu5F9-G4) Cycle 1 doses will be administered on Days 8 and 22, while doses in Cycles 2+ will be administered on Days 1 and 15. Drugs should not be co-administered through the same IV line.

Part 2 Dose: Avelumab will be dosed based on the final dose selection that will be made by the CTSC after all available clinical, CCI and PK data are reviewed from Part 1.

On days when both study drugs are given, Hu5F9-G4 will be administered at least 1–2 hours after the completion of the avelumab infusion.

Study Endpoints

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

Statistical Methods and Analyses

Safety: 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 for patients in Part 1, TEAEs (AEs worsening or occurring during or after a patient's first exposure to study drug), study drug-related adverse events, vital signs, physical examinations, laboratory, and ADA assessments. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 19.0) and grouped by system organ class and preferred term. Summary tables will include the number and percentage of patients with AEs, serious adverse events (SAEs), fatal AEs, and other AEs of interest.

Data will be presented by Part 1 (Safety Run-in Cohort) and by Part 2 (Ovarian Cancer Expansion Cohort), and, where relevant, summarized across various dose cohorts.

Efficacy: The efficacy analyses will include analysis of the outcome measures of overall response rate (ORR) using RECIST and irRECIST, duration of response (DOR), time to progression (TTP), progression-free survival (PFS), and overall survival (OS). ORR will be summarized by frequency and percentages along with 95% exact confidence interval. The time-to-event endpoints of DOR, TTP, PFS, and OS will be summarized using Kaplan-Meier methods. Additional details will be provided in the Statistical Analysis Plan (SAP).

Pharmacokinetics: Based on the distinct MOAs of Hu5F9-G4 and avelumab, drug-drug PK interactions are not expected. Thus, samples for PK analysis for avelumab will be biobanked and will be analyzed based on CTSC recommendation. Summaries of PK concentration data and PK parameters will be provided. Due to the sparse sampling regime, it is anticipated that the maximum serum concentration (C_{max}) after the first dose will be the only calculable PK parameter in this population.

Immunogenicity Analyses: The rate and magnitude of anti-Hu5F9-G4 antibody positivity will be evaluated for all patients in Parts 1 and 2 of the trial, and for the pooled patient population. CCI [redacted] Immunogenicity analysis may also be performed for avelumab. However, it is not expected that Hu5F9-G4 will impact the immunogenicity of avelumab and vice versa.

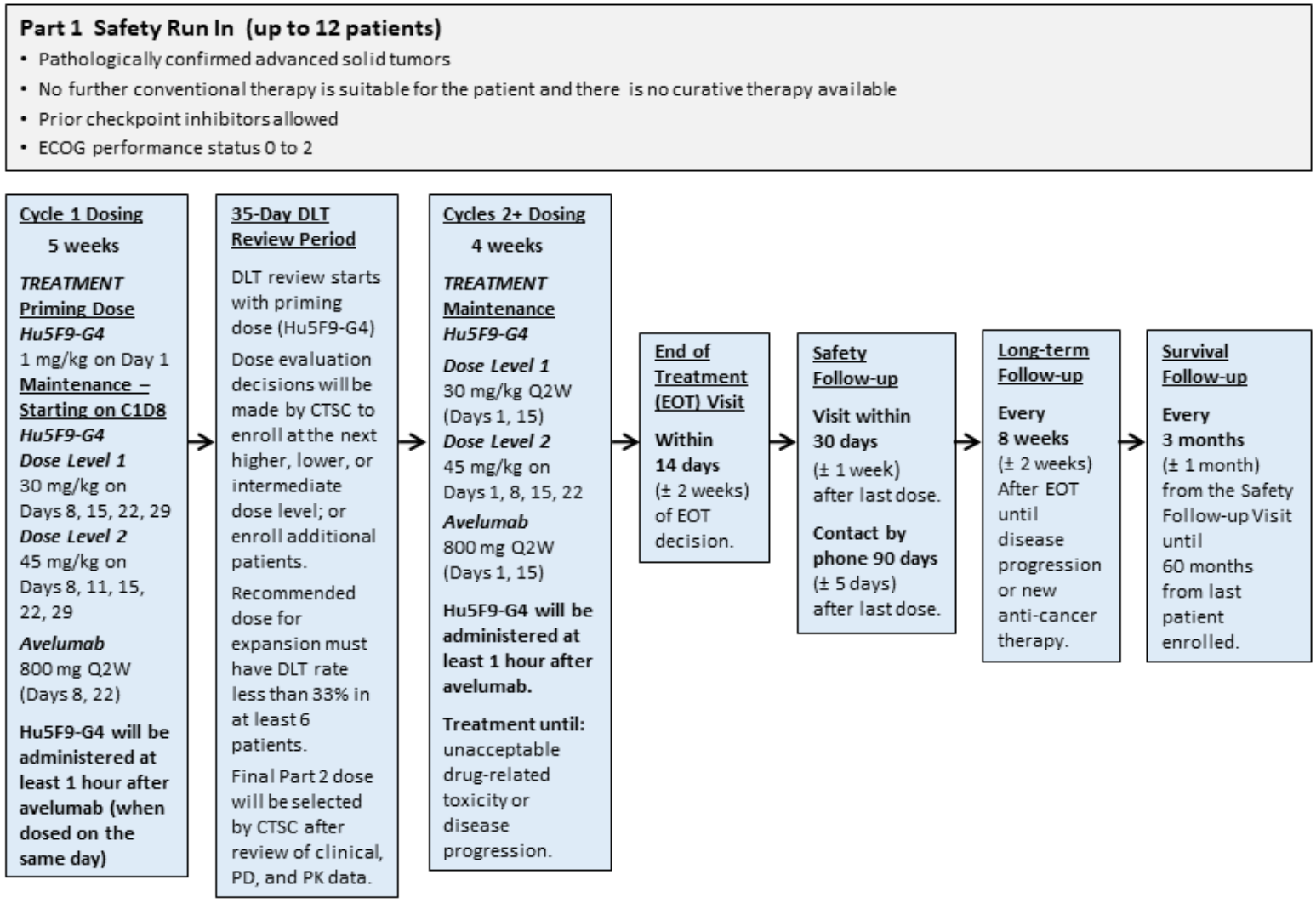
CCI [redacted]

Sample Size Determination:

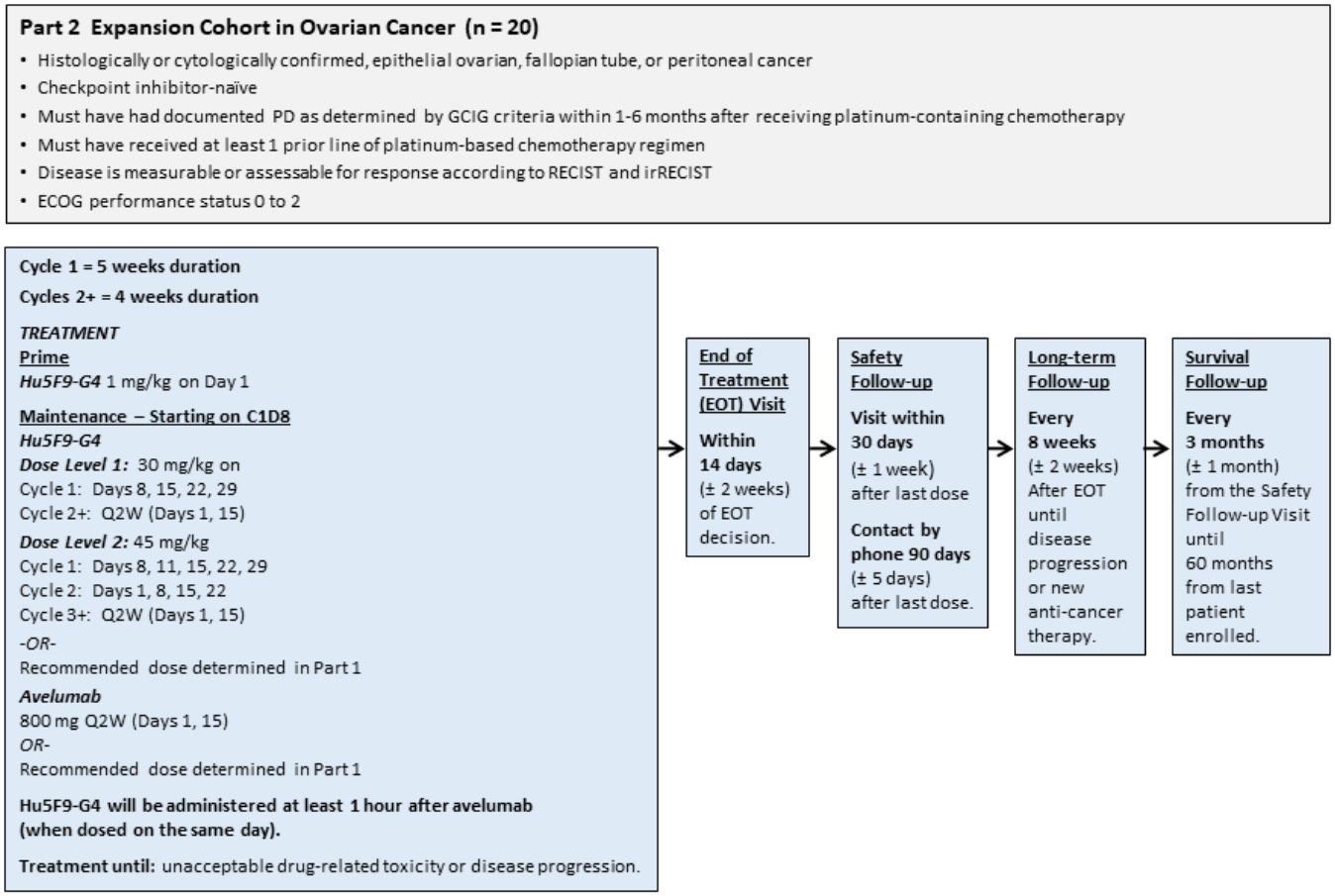
This trial will include a total of up to 40 patients. This sample size includes both Parts 1 and 2 of the study, allowing for patient replacement as defined in this protocol. In Part 1, up to 12 -18 patients will be treated in a Safety Run-in Cohort, assuming that no more than 2 DLTs in each cohort of 6 patients occur. Up to 18 patients may be enrolled in Part 1 if some patients are ineligible for DLT assessment.

Part 2 consists of a single expansion cohort in 20 ovarian cancer patients who will undergo safety, PK, CCI [redacted]. Each dose level tested in Part 2 will enroll 20 patients. This sample size will allow for confirmation of the safety profile of Hu5F9-G4 and avelumab in this population, and the mandatory tumor biopsies CCI [redacted]. The anti-tumor activity of this regimen will also be documented. With this sample size, the lower bound of the 95% exact confidence interval would exclude 10% if the objective response rate is 30% or higher.

STUDY DESIGN SCHEMA, PART 1



STUDY DESIGN SCHEMA, PART 2



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ABBREVIATIONS AND DEFINITIONS

ABO	any of the four blood groups A, B, AB, and O comprising the ABO system
ADA	anti-drug antibodies
ADL	activities of daily life
AE	adverse event
AHA	American Heart Association
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
BRCA	breast cancer susceptibility gene
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CFR	Code of Federal Regulations
C_{max}	maximum concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CRO	clinical research organization
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
CTSC	Clinical Trial Steering Committee
DAT	direct antiglobulin test
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EAS	Efficacy Analysis Set
ECG	electrocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGA	EDTA/glycine-acid
EDC	electronic data capture
ELISA	enzyme linked immunosorbent assay
EOT	End of Treatment
ESC	European Society of Cardiology
FDA	Food and Drug Administration
GCIG	Gynecologic Cancer InterGroup
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	intensive care unit
IEC	Independent Ethics Committee
INFg	interferon gamma
INR	international normalized ratio
irPD	progressive disease according to irRECIST (Bohnsack 2014)
irRECIST	Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-related Response Criteria
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intra-uterine device
IUS	intra-uterine hormone-releasing system
IV	intravenous
kg	kilogram
KM	Kaplan-Meier
L	liters
LDH	lactate dehydrogenase
LHRH	luteinizing-hormone releasing hormone
LISS	low ionic strength solution
LTFU	long-term follow-up
LPE	last patient enrolled

LSC	leukemic stem cells
M1	macrophages that suppress tumor progression
M2	macrophages that promote tumor progression
mAb	monoclonal antibody
MCC	Merkel cell carcinoma
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary of Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MOA	mechanism of action
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NSG	NOD/SCID/IL2R gamma null
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PARP inhibitors	polyadenosine-diphosphate ribose polymerase inhibitors
PAS	Pharmacokinetic Analysis Set
PD	progressive disease
PD-1	programmed cell death-protein 1
PD-L1	programmed cell death-ligand 1
PeG	polyethylene glycol
PFI	platinum-free interval
PFS	progression-free survival
PI	Prescribing Information
PK	pharmacokinetic(s)
PR	partial response
PRBC	packed red blood cell (transfusions)
PT	prothrombin time
RANKL	receptor activator of nuclear factor kappa-B ligand
RBC	red blood cell
REC	Research Ethics Committee

RECIST	Response Evaluation Criteria in Solid Tumors
Rh	Rhesus factor
RO	Receptor Occupancy
RP2DS	recommended Phase 2 dose and schedule
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety Analysis Set
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIRPα	signal regulatory protein alpha
SOA	Schedule of Assessments
S-P	Ser-Pro
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
TTP	time to tumor progression
UK	United Kingdom
ULN	upper limit of normal
US	United States
WBC	white blood cell

1. BACKGROUND

1.1. Ovarian Cancer

Ovarian cancer is the most frequent cause of gynecologic cancer deaths in the United States (US). Standard of care for this disease in the frontline and platinum-sensitive recurrent setting is platinum-based chemotherapy with or without antiangiogenic agents. More recently, targeted agents such as poly adenosine-diphosphate ribose polymerase (PARP) inhibitors have been approved by the Food and Drug Administration (FDA) for women with breast cancer susceptibility gene (BRCA) mutations and/or alterations in the homologous recombination pathway. Experience with newer immunotherapies in this disease, such as the checkpoint inhibitors, has not yet matured to impact clinical outcomes. In women with recurrent ovarian cancer, the platinum-free interval (PFI), defined as the interval between the last platinum dose and the date of relapse (Rustin 2011), is strongly correlated with the likelihood of response to subsequent chemotherapy. Patients who initially respond to systemic therapy with a PFI greater than 1 month, but less than 6 months, have been historically referred to as platinum-resistant, and these patients have limited treatment options (Davis 2014). Thus, the development of effective cancer treatments for this patient population would address a substantial unmet medical need.

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

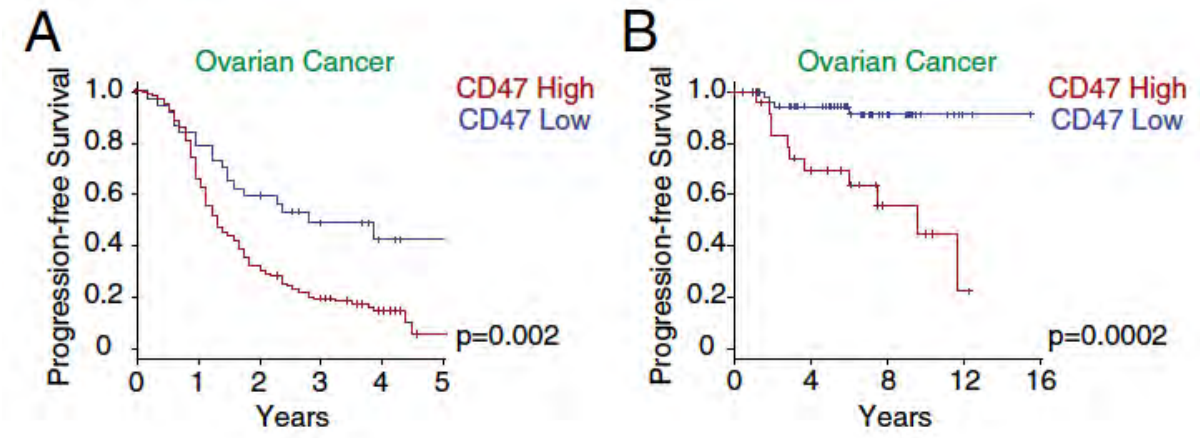
1.2.1. CD47 Biology

CD47 is a widely-expressed cell surface protein that regulates 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 (RBCs) (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 ovarian 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, prostate, and colon cancer (Willingham 2012). In 2 distinct datasets derived from patients with ovarian cancer, tumor CD47 messenger ribonucleic acid (mRNA) expression levels correlated with worse progression-free survival (PFS) and overall survival (OS), as shown in Figure 1-1.

Figure 1-1. CD47 mRNA Expression Levels May be a Prognostic Factor



Source: Willingham 2012.
A = Data from 269 ovarian cancer patients, hazard ratio for progression-free survival (PFS) = 2.1 (95% confidence interval [CI]: 1.3—3.3).
B = Data from 83 ovarian cancer patients, hazard ratio for PFS = 6.6 (95% CI: 2.1—20.8).

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. 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 phagocytic 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. In summary, antibody blockade of the CD47/SIRPα pathway serves as a promising therapeutic strategy in cancer.

1.2.2. Hu5F9-G4

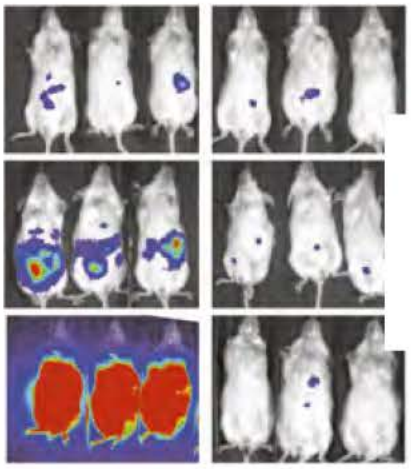
Hu5F9-G4 is a humanized anti-human IgG4 monoclonal antibody (mAb) that binds to CD47 and blocks its interaction with its receptor, enabling phagocytosis of human cancer cells (Liu 2015b). The activity of Hu5F9-G4 is primarily dependent on blocking CD47 binding to SIRPα and not on the recruitment of Fc-dependent 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 (Liu 2015b). 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 of 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 ovarian cancer laboratory models, anti-CD47 antibodies enhance the in vitro phagocytosis of ovarian cancer stem cells by macrophages and they also inhibit the in vivo growth of engrafted ovarian tumor cells (Figure 1-2).

Figure 1-2. Anti-CD47 Antibody Therapy Eliminates Ovarian Cancer Cells *In Vivo* and Cures Mice Xenografted with Patient Ovarian Cancer



Anti-CD47 monoclonal antibodies (mAbs) inhibit tumor growth as measured by bio-luminescence activity (Left Panel) and improve survival (Right Panel) of NOD/SCID/IL2R gamma null (NSG) mice engrafted with ovarian cancer (Willingham 2012).

1.2.4. Hu5F9-G4 Clinical Studies

1.2.4.1. Summary of Hu5F9-G4 Clinical Safety

As of 24 July 2017, a total of 92 patients have been treated with Hu5F9-G4 both as monotherapy and in combination. Dose levels evaluated to date are described in Section 1.6.1, Starting Dose Rationale.

Two monotherapy Phase 1 clinical trials are ongoing. The first-in-human study, Study SCI-CD47-001, is a Phase 1 dose escalation trial of Hu5F9-G4 in patients with advanced solid tumors and lymphomas. The Phase 1 study was designed to determine the optimal dose and schedule of Hu5F9-G4 and to characterize its

preliminary safety, pharmacokinetics (PK), and pharmacodynamics. As of 24 July 2017, this trial has treated 58 patients and dose escalation is ongoing. The second study, Study SCI-CD47-002, is a Phase 1 trial in patients with relapsed or refractory AML and subsequently relapsed or refractory myelodysplastic syndrome (MDS). The second study was initiated to define the maximum tolerated dose (MTD) and to evaluate the safety, PK, and pharmacodynamics of Hu5F9-G4 in this patient population. This trial has treated 14 patients as of 24 July 2017 and it is also ongoing.

In monotherapy trials with Hu5F9-G4, the most common clinically relevant non-serious adverse drug reaction is an acute mild anemia observed after the first dose of study drug. This clinical observation is consistent with the known MOA of Hu5F9-G4 and the physiologic role of CD47 in regulating the turnover of aging erythrocytes. However, in solid tumor and lymphoma patients, the clinical impact of this anemia has been substantially mitigated using a priming and maintenance dosing strategy. After an initial priming dose of 1 mg/kg of Hu5F9-G4 administered intravenously (IV) on Day 1 of Week 1, a rapid, predictable fall in hemoglobin level of 1.5 to 2 g/dL on average is observed during the first 1 to 2 weeks of treatment. Beginning in Week 2, substantially higher maintenance doses of Hu5F9-G4 can be administered with no further effects on RBCs. In solid tumor and lymphoma patients, this mild acute anemia is followed by a rapid, compensatory reticulocytosis and a gradual return of hemoglobin levels to baseline by Week 3 or 4, despite continued dosing. In patients with AML with significant disease bone marrow infiltration, a similar mild acute anemia with an average hemoglobin decrement of 0.5 to 2 g/dL is observed; however, these patients are easily managed with RBC transfusions despite continued treatment with Hu5F9-G4. Other laboratory abnormalities associated with Hu5F9-G4 including reticulocytosis, spherocytosis, transient hyperbilirubinemia (predominantly unconjugated), and decreased haptoglobin are all indicative of extravascular hemolysis consistent with phagocytic removal of RBCs after CD47 blockade.

Another erythrocyte-associated drug effect is hemagglutination, which typically occurs within 24 hours of the first or second dose of Hu5F9-G4. In solid tumor patients, this transient hemagglutination is observed less frequently beyond the first 1 or 2 infusions. The clinical relevance of this hemagglutination is uncertain, as it has not been correlated with any clinical signs or symptoms. Because RBC agglutination may be related to the rapid rise in Hu5F9-G4 concentrations in treatment-naïve patients, the duration of the initial priming dose infusion may have relevance. In solid tumor patients, a single 1-hour priming dose infusion of 1 mg/kg of Hu5F9-G4 was associated with hemagglutination in 6 out of 6 patients. However, when the duration of the 1 mg/kg priming dose was extended to 3 hours in subsequent patients, hemagglutination only occurred in 6 out of 14 patients. Currently, a 3-hour priming dose infusion duration is being used in all solid tumor and lymphoma patients; however, a shorter 2-hour infusion duration is being used for subsequent maintenance doses. In the AML trial, a 3-hour infusion is being used for all Hu5F9-G4 doses ≥1.0 mg/kg.

Other common treatment-related adverse events (AEs) include headache, fatigue, nausea, photopsia, urine discoloration, low back pain, and abdominal pain. Common drug-related abnormal laboratory findings include transient reticulocytosis, spherocytosis, hyperbilirubinemia (predominantly unconjugated), D-dimer elevation, and decreased haptoglobin. In solid tumor patients, the D-dimer elevation has not been any associated with any signs of disseminated intravascular coagulation, thrombocytopenia, coagulopathy, microangiopathy, or thromboembolic disease. The majority of these findings occur following the first infusion with relatively fewer drug-related toxicities reported beyond the first cycle. In solid tumor patients, maintenance doses of up to 30 mg/kg once weekly have been explored with dose escalation continuing. Since the adoption of an Hu5F9-G4 priming and maintenance dosing strategy, no MTD level has been identified. In AML patients, twice-weekly treatments with Hu5F9-G4 coupled with an intrapatient dose escalation scheme has also been well tolerated with no dose-limiting toxicities (DLTs) being reported to date. Dose escalation is also ongoing in the AML Phase 1 trial.

Two combination clinical trials have been initiated with Hu5F9-G4. The first study (Study 5F9003) has treated 11 patients with NHL in combination with rituximab, while the second (Study 5F9004) has treated 9 colorectal cancer (CRC) or solid tumor patients with Hu5F9-G4 and cetuximab. Both of these combination studies are continuing to escalate the doses of these agents in combination; an MTD has not been reached. As of 24 July 2017, no new major toxicities of these combinations have been observed, and there is no evidence that Hu5F9-G4 alters the toxicity profile of rituximab or cetuximab.

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 ongoing solid tumor Phase 1 clinical trial (SCI-CD47-001), 5 patients with advanced ovarian cancer or related gynecologic tumors have been treated with doses of Hu5F9-G4 of 20 mg/kg or higher. Doses of 20 and 30 mg/kg generate consistent trough Hu5F9-G4 serum concentrations greater than 100 mcg/mL, which was the minimum concentration threshold associated with preclinical anti-tumor activity (Forty Seven Inc., data on file). Four of these five patients demonstrated a fall in CA125, commensurate with the start of Hu5F9-G4 monotherapy. Two of these patients had confirmed objective partial responses (PRs). Both were heavily pretreated with PPD including PPD . One patient was a PPD woman with PPD whose CA125 decreased from PPD and who also had a PPD tumor measurements on her initial PPD restaging scans. She remained on study PPD before progression of disease. The second patient was a PPD woman with PPD who had a decrease in CA125 from PPD and demonstrated a PPD . She remains on active treatment for PPD . Of the 3 remaining ovarian cancer patients, 2 had stable disease (SD) and 1 had progressive disease (PD) as their best RECIST responses. Hu5F9-G4

shows monotherapy activity in ovarian and related gynecologic cancers; thus, an expansion of the clinical experience in this disease setting is warranted.

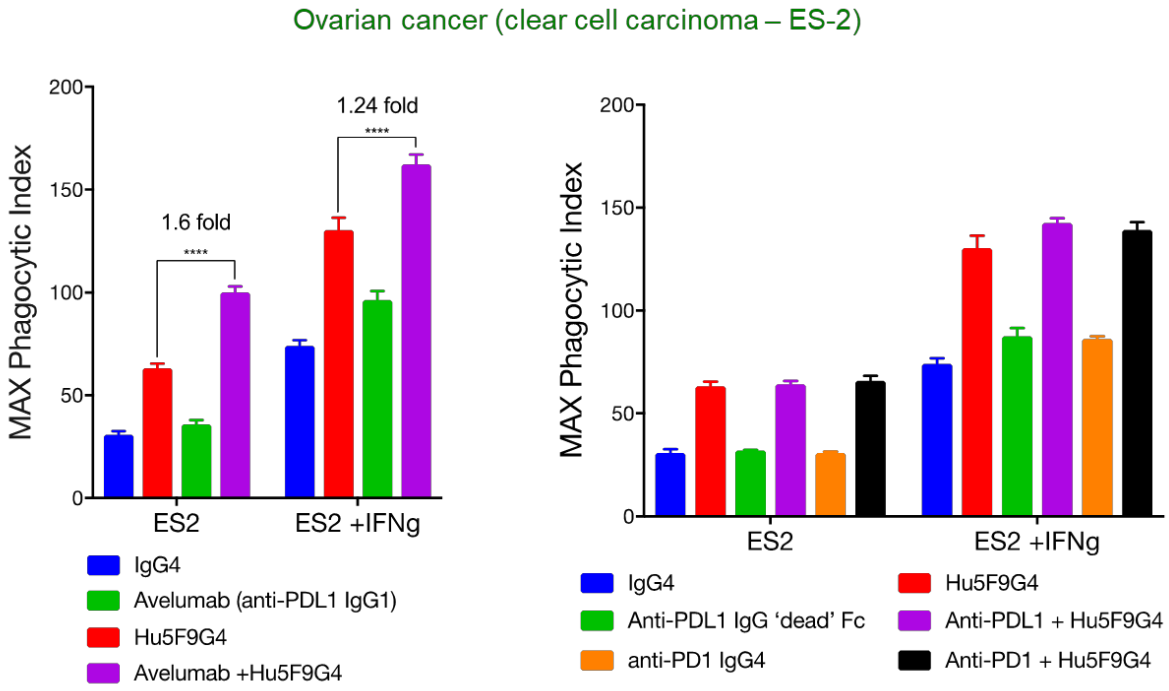
In Study SCI-CD47-002, 2 patients with relapsed/refractory AML treated with Hu5F9-G4 10 mg/kg administered twice weekly have demonstrated marked reduction in bone marrow cellularity after 4 weeks of treatment. One of these patients also had a greater than 50% reduction in the percent AML blasts in the bone marrow and this patient remains stable on treatment for over 44 weeks. Interestingly, this same patient demonstrated an increase in bone marrow infiltration by CD3-positive lymphocytes from 10–15% to 40–50% of bone marrow cells by Day 53 of treatment. This provides preliminary support for the hypothesis that CD47-blockade with Hu5F9-G4 may enhance an adaptive T-cell response to tumor antigens. Such observations support the clinical evaluation of Hu5F9-G4 in combination with programmed cell death-ligand 1 (PD-L1) checkpoint inhibitors in clinical trials.

Early evidence of anti-tumor activity for Hu5F9-G4 in combination with anti-tumor antibodies is also emerging. In the 5F9003 NHL combination study, a heavily pretreated patient with follicular lymphoma treated with 10 mg/kg of Hu5F9-G4 combined with standard doses of rituximab achieved a complete response (CR) and has remained on treatment for longer than 39 weeks. In addition, objective anti-tumor responses were observed in 2 patients with diffuse large B-cell lymphoma (DLBCL) treated with 20 mg/kg of Hu5F9-G4 and rituximab including a CR and a PR. Both previously received rituximab-containing regimens. Finally, in the 5F9004 solid tumor/CRC study, 1 CRC patient treated with 10 mg/kg of Hu5F9-G4 with 400/250 mg/m^2 of cetuximab has achieved a confirmed PR. Dose escalation in both the NHL and CRC combination trials are ongoing. These emerging data suggest that combination regimens with Hu5F9-G4 are well tolerated and have potential for therapeutic benefit in patients with solid tumors and lymphomas. Thus, exploration of additional novel Hu5F9-G4 combinations with other monoclonal antibodies, including PD-L1 inhibitors, is warranted.

1.3. Preclinical Combination Studies

Antibodies such as avelumab with an active Fc component may be optimal for combining with anti-CD47 targeting agents. Avelumab can bind to PD-L1 on the surface of cancer cells, thereby providing an exogenous pro-phagocytic signal that can be augmented by CD47 blockade. In contrast, anti-PD-L1 antibodies that lack Fc component activity and anti-programmed cell death-protein 1 (PD-1) antibodies that do not bind directly to cancer cells do not provide enhancement of pro-phagocytic signals. This is demonstrated in preclinical studies, showing that the combination of avelumab with Hu5F9-G4 enhances antibody-dependent cellular phagocytosis (ADCP) of PD-L1 expressing ES-2 ovarian cancer cells (Forty Seven Inc., data on file; Figure 1-3, left panel). This occurs both at baseline and after treatment of cancer cells with interferon gamma (INFg) to enhance PD-L1 expression. However, when checkpoint signaling is blocked using other inhibitors such as an anti-PD-L1 antibody with a “dead” Fc component or an anti-PD-1 antibody that does not bind cancer cells, no enhancement of phagocytosis occurs in combination with Hu5F9-G4 (Figure 1-3, right panel). In contrast to avelumab, these other PD-L1/PD-1 inhibitors cannot provide additional pro-phagocytic signals. Currently this combination with avelumab has only been evaluated in this ovarian cancer model, but it has the potential to apply to other tumor types as well. These data suggest that the unique combination of Hu5F9-G4 with avelumab may have additional beneficial anti-tumor properties that can be explored in the clinical setting.

Figure 1-3. Avelumab but Not Other Checkpoint Inhibitor Antibodies Enhance Phagocytosis of Cancer Cells in Combination with Hu5F9-G4



ES-2 ovarian cancer cells express high levels of PD-L1 and INFg pre-incubation can enhance PD-L1 expression

Source: Forty Seven Inc., Report Numbers FSI-2017-004 and FSI-2017-005.
Abbreviations: IFNg = interferon gamma; PD-L1 = programmed death ligand-1.

1.4. Translational Studies Background

Blockade of the CD47-SIRPα signaling axis on tumor cells by a monoclonal anti-CD47 antibody could lead 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 intra-tumoral 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. 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. Avelumab

The PD-1 receptor and PD-1 ligands 1 and 2 (PD-L1, PD-L2) play integral roles in immune regulation. Expressed on activated T cells, PD-1 is activated by PD-L1 and PD-L2 expressed by stromal cells, tumor cells, or both, initiating T-cell death and localized immune suppression (Dong 1999; Freeman 2000; Dong 2002; Topalian 2012a), potentially providing an immune-tolerant environment for tumor development and growth. Conversely, inhibition of this interaction can enhance local T-cell responses and mediate anti-tumor activity as demonstrated in nonclinical animal models (Dong 2002; Iwai 2002).

In the clinical setting, treatment with antibodies that block the PD-1–PD-L1 interaction have been reported to produce objective response rates of 7% to 38% in patients with advanced or metastatic solid tumors, with tolerable safety profiles (Brahmer 2012; Topalian 2012b; Hamid 2013). Notably, responses appeared prolonged, with durations of 1 year or more for the majority of patients.

Avelumab is a fully human monoclonal antibody of the immunoglobulin (Ig) G1 isotype. This anti-PD-L1 therapeutic antibody concept is being developed in oncological settings by Merck KGaA (Darmstadt, Germany), its subsidiary, EMD Serono Research & Development Institute, Inc. (Billerica, MA, USA), and by Pfizer, Inc. (New York, NY, USA).

Avelumab selectively binds to PD-L1 and competitively blocks its interaction with PD-1. Compared with anti-PD-1 antibodies that target T-cells, avelumab targets tumor cells. It is therefore hypothesized to have fewer side effects, including a lower risk of autoimmune-related safety issues, since the blockade of PD-L1 leaves the PD-L2 / PD-1 pathway intact to promote peripheral self-tolerance (Latchman 2001). For additional details from the in vitro and nonclinical studies, refer to the current Avelumab Investigator's Brochure (Avelumab IB).

Avelumab is currently in clinical development in several ongoing Phase 1 to 3 clinical trials. Avelumab is being investigated as a monotherapy or in combination with other anti-cancer treatments in patients with different types of malignancies.

The clinical experience of avelumab, including its clinical activity, safety, PK, and pharmacodynamics, is currently based largely on data from Trial EMR100070-001, which is a Phase 1, open-label, multicenter trial being conducted in over 1600 patients with solid tumors. Study EMR100070-001 has 2 phases, a dose escalation phase and a treatment expansion phase, the latter recruiting patients in 16 different solid tumor expansion cohorts.

Avelumab exposure parameters, including the C_{max} and the area under drug concentration curve (AUC), generally increased in an approximately dose-proportional manner. The terminal half-life of avelumab increased with avelumab doses. There was little accumulation of avelumab, which was consistent with the short half-life of avelumab.

Clinical activity with avelumab has been observed in patients with different types of solid tumors. In patients with recurrent or refractory ovarian cancer, avelumab demonstrated an acceptable safety profile and evidence of clinical activity (Disis 2016). In 124 women participating in an ongoing Phase 1b avelumab study, 12 achieved PR (9.7%) and 55 achieved SD (44.4%). The median PFS was 11.3 weeks and the OS was 10.8 months. Additional details are provided in the Avelumab IB. In addition, two large Phase 3 trials of avelumab in ovarian cancer are ongoing. The first is a study of avelumab either in combination with or following carboplatin and paclitaxel chemotherapy in previously untreated epithelial ovarian, fallopian tube cancer, or primary peritoneal cancer patients (JAVELIN Ovarian 100; NCT02718417; Appendix A).

Available safety data for the avelumab program, which are summarized in the current IB, demonstrate an acceptable safety profile with 10 mg/kg of avelumab. The safety data from patients with different tumor types treated with avelumab suggest an acceptable safety profile of the compound. Most of the observed events were either in line with those expected in patients with advanced solid tumors or with similar class effects of mAb blocking the PD-1/PD-L1 axis. Infusion-related reactions, including drug hypersensitivity reactions and immune-mediated adverse

reactions (immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies [thyroid disorders, adrenal insufficiency, new onset type I diabetes mellitus, pituitary disorders]), immune-related nephritis and renal dysfunction, and other immune-related AEs (myositis, myocarditis, Guillain-Barré syndrome, uveitis) have been identified as important risks for avelumab. Detailed guidelines for the management of immune-related adverse events and infusion-related reactions have been implemented in all ongoing clinical studies with avelumab, including the current protocol (Section 6.5.2).

1.6. Starting Dose Rationale

1.6.1. Hu5F9-G4 Dose

The following starting Hu5F9-G4 dosing scheme is proposed for this study: In Cycle 1, a priming dose of 1 mg/kg on Day 1 of Week 1, followed by doses of 30 mg/kg on Day 8, 15, 22, 29 (Weeks 2-5). This is followed by doses of 30 mg/kg Q2W on Days 1 and 15 beginning in Cycle 2.

The safety and PK of Hu5F9-G4 has been explored in solid tumor and lymphoma patients using a priming and maintenance dose schedule (Forty Seven Inc., data on file; Section 1.2.4). In the ongoing solid tumor Phase 1 study, a dosing schedule that includes an initial priming dose of 1 mg/kg administered on Day 1 of Week 1, with 2 subsequent doses of 30 mg/kg in Week 2, followed by weekly doses of 30 mg/kg beginning in Week 3, has been demonstrated to be safe as monotherapy. No maximum tolerated dose (MTD) has been reached in any study with up to 45 mg/kg of weekly dosing as monotherapy (Study SCI-CD47-001; data on file at Forty Seven Inc.). Additionally, Hu5F9-G4 has been well-tolerated in combination with other monoclonal antibodies (including rituximab and cetuximab) with no MTD reached with up to 30 mg/kg of weekly dosing. After priming doses of 1 mg/kg, mean reduction of approximately 2 g/dL in hemoglobin was observed, followed by a rapid associated reticulocytosis. CD47 receptor occupancy (RO) assays also confirmed near 100% occupancy of CD47 on RBCs by Hu5F9-G4 at this dose. Thus, 1 mg/kg was identified as the optimal Hu5F9-G4 priming dose.

In the solid tumor study (Study SCI-CD47-001), at doses of 30 mg/kg of circulating Hu5F9-G4, drug concentrations were in the range of 400–1500 mcg/mL by the end of the first cycle—far exceeding concentrations associated with anti-tumor efficacy in preclinical xenograft models (100 mcg/mL; Forty Seven Inc. data on file) and also higher than the concentrations at 20 mg/kg (250–900 mcg/mL), which was associated with objective responses in 2 patients. Population PK modelling and simulation predicts that with the proposed dosing regimen of 30 mg/kg weekly loading doses followed by 30 mg/kg every 2 weeks maintenance doses, the steady-state concentrations will be in the range of 300 to 1000 mcg/mL. This concentration range has been associated with objective response in 2 patients with ovarian cancer in Study SCI-CD47-001. Model-predicted and observed receptor occupancy on peripheral white blood cells (WBCs) at these concentrations was near maximal. The dose regimen of 30 mg/kg of Hu5F9-G4 every 2 weeks starting in Cycle 2 proposed for this study is expected to achieve optimal impact on the molecular target and be both safe and efficacious.

This study proposes to evaluate the dose regimen described above, which is the recommended Phase 2 dose of Hu5F9-G4, in combination with standard approved doses of avelumab in a 12-patient Safety Run-in Cohort. If the safety of this combination is confirmed, the regimen will be evaluated further in an expansion cohort of 20 ovarian cancer patients. No synergistic toxicities for the 2 agents in combination are anticipated; however, if DLTs are observed at the initial starting dose, dose de-escalation of Hu5F9-G4 may be explored (as described in Section 3) to define an MTD.

Further dose escalation to 45 mg/kg was performed in six patients and considered safe with no DLT's in Study SCI-CD47-001. As such, if no DLTs are reported and Dose Level 1 is considered safe, the dose of Hu5F9 may be escalated to 45 mg/kg. (See Table 3-1) in Part A. The CTSC may recommend one or multiple doses and schedules to be tested in Part 2. Each dose tested will enroll a total of 20 patients.

1.6.2. Avelumab Dose

To date, avelumab has been administered at the clinically active tolerable dose of 10 mg/kg every 2 weeks to more than 1800 patients across multiple indications. Furthermore, this 10 mg/kg every-2-week avelumab dosing regimen has been approved by the FDA as the first treatment for Merkel Cell Carcinoma and Urothelial Carcinoma. Avelumab was originally dosed on a mg/kg basis in order to reduce inter participant variability in drug exposure. However, emerging data for monoclonal antibodies, including the marketed PD-1 and PD-L1 immune checkpoint inhibitors nivolumab, pembrolizumab, and atezolizumab, reveal that body weight-based dosing regimens do not result in less variability in measures of exposure over fixed (i.e., body-weight independent) dosing regimens (Wang 2009; Freshwater 2017; Zhao 2017). Additionally, fixed dosing offers the advantages of less potential for dispensing errors, shorter dose preparation times in a clinical setting, and greater ease of administration.

Population PK analysis was conducted based on the acquired data across 3 single-agent avelumab studies in more than 1700 patients with 14 different types of cancer. Pharmacokinetic simulations suggest that exposures to avelumab across the available range of body weights are less variable with 800 mg every 2 weeks compared with 10 mg/kg every 2 weeks; exposures were similar near the population median weight. Low-weight participants tended towards marginally lower exposures relative to the rest of the population when weight-based dosing was used, and marginally higher exposures when flat dosing was applied. However, the implications of these exposure differences are not expected to be clinically meaningful at any weight across the entire population. Furthermore, the 800 mg every 2-week dosing regimen is expected to result in C_{trough} > 1 µg/mL required to maintain avelumab serum concentrations at > 95% target occupancy throughout the entire 2-week dosing interval in all weight categories.

Therefore, in this clinical study, a fixed dosing regimen of 800 mg administered as 1-hour IV infusion every 2 weeks will be used for avelumab.

1.7. Study Rationale and Risk-Benefit

Patients with advanced ovarian cancer who have relapsed or are resistant or refractory to platinum-based chemotherapy have limited options for effective treatment and an overall poor prognosis (Davis 2014). Consequently, a well-tolerated immunotherapy combination that can induce anti-tumor responses and prolong PFS and OS would be an important therapeutic advance in the management of disease in these patients. Preliminary clinical data from Hu5F9-G4 monotherapy in patients with solid tumors suggest that blockade of CD47 may induce objective responses in heavily pretreated patients with ovarian cancer. Furthermore, preclinical studies and our understanding of the mechanism of Hu5F9-G4 action suggest that targeting CD47 may generate substantial synergistic anti-tumor activity when combined with PD-L1 checkpoint inhibitors. Thus, the scientific rationale for exploring the efficacy of this combination in this setting is strong.

The clinically relevant overlapping toxicities that have been observed for both Hu5F9-G4 and avelumab are infusion-related reactions and immune-related AEs. Single-agent toxicity data are summarized in Section 1.2.4.1 for Hu5F9-G4 and in Section 1.5 for avelumab. The safety risk of the proposed combination is not anticipated to be greater than that associated with the use of either of these agents as monotherapy. However, because the preclinical safety experience with this combination is limited and there is potential for overlapping toxicity, data from a Safety Run-in Cohort will be evaluated before treating additional patients with advanced ovarian cancer.

The combination of Hu5F9-G4 and avelumab in patients with platinum-resistant advanced ovarian cancer has the potential to address an unmet medical need by enhancing anti-tumor activity with the expectation of a manageable safety profile.

2. STUDY OBJECTIVES AND ENDPOINTS

The objectives and endpoints for the study are summarized in Table 2-1. Information about study assessments and procedures is provided in Section 7; assessment of safety is provided in Section 9; measurement of effect is provided in Section 10; and statistical analysis information is provided in Section 11.

Table 2-1. Objectives and Endpoints

PRIMARY	
OBJECTIVES	**ENDPOINTS**
Safety Run-in Cohort: To investigate the safety and tolerability of Hu5F9-G4 in combination with avelumab in patients with advanced solid tumors **Ovarian Cancer Expansion Cohort**: To confirm the safety and tolerability of this combination and evaluate the anti-tumor activity based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer 2009) in patients with checkpoint inhibitor-naïve ovarian cancer, fallopian tube cancer, and primary peritoneal carcinoma who have previously progressed within 1-6 months of receiving platinum chemotherapy	AEs and DLTs graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 (Appendix C) or customized AE severity grading for hemagglutination and microangiopathy, as defined in Section 6.5.1.3 (Safety Management Guidelines) Objective response as defined by the Investigator according to RECIST v1.1 (Eisenhauer 2009)
SECONDARY	
OBJECTIVES	**ENDPOINTS**
Safety Run-in Cohort: To determine a recommended dose of Hu5F9-G4 + avelumab in patients with solid tumors To examine the pharmacokinetic (PK) profile of Hu5F9-G4 in combination with avelumab To evaluate the immunogenicity of Hu5F9-G4 in combination with avelumab	Recommended Phase 2 dose and schedule (RP2DS) of Hu5F9-G4 in combination with avelumab Serum concentrations of Hu5F9-G4 collected at selected time points Anti-drug antibodies (ADA) to Hu5F9-G4

Ovarian Cancer Expansion Cohort: To evaluate the anti-tumor activity of Hu5F9-G4 in combination with avelumab in all patients using the Immune Response Evaluation Criteria in Solid Tumors (irRECIST; Bohnsack 2014) and, where applicable, the Gynecologic Cancer Intergroup (GCIG) response criteria (Rustin 2011) To assess additional efficacy endpoints including duration of response (DOR), time to tumor progression (TTP), progression-free survival (PFS), and overall survival (OS) To evaluate the impact of Hu5F9-G4 in combination with avelumab on the myeloid cell populations in the tumor microenvironment, as assessed in sequential tumor biopsies in patients with platinum-resistant ovarian cancer	**Ovarian Cancer Expansion Cohort**: Objective response, as defined by the Investigator according to irRECIST (Bohnsack 2014) and GCIG response criteria (Rustin 2011) For patients who respond, DOR will be evaluated. For all patients, efficacy endpoints will include TTP, PFS, and OS. Immunohistochemical staining of myeloid cells in formalin-fixed, paraffin-embedded tissues
CCI [redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3. STUDY DESIGN

3.1. Overall Study Design

This is an open label, multicenter, Phase 1b trial investigating the combination of Hu5F9-G4 and avelumab in patients with solid tumors and checkpoint inhibitor-naïve ovarian cancer who progress within 1-6 months of receiving platinum-containing chemotherapy. Checkpoint inhibitor-naïve patients are defined as those patients who have not been previously treated with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody (including ipilimumab, tremelimumab, or any other antibody or drug specifically targeting T-cell co-regulatory proteins). The study will be conducted in 2 parts:

Part 1–Safety Run-in Cohort: Patients with solid tumors will be treated at the starting dose with Hu5F9-G4 + avelumab to examine the safety and PK of this study drug combination.

Part 2–Expansion Cohort: Patients with checkpoint inhibitor-naïve ovarian cancer will be treated with Hu5F9-G4 + avelumab to evaluate the safety, efficacy, CCI [redacted] effects of this study drug combination.

Patients may continue treatment unless they develop unacceptable toxicities that cannot be clinically managed by dose or schedule modifications as outlined in Section 6.4, or if they have confirmed PD according to Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST; Bohnsack 2014) as described in Section 10.1.

Hu5F9-G4 and avelumab combination treatment may continue past the initial determination of disease progression according to irRECIST 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)

If disease progression is due to brain metastasis, patients may continue avelumab treatment after the local treatment of the brain lesions provided that the above criteria are met in addition to the following and in consultation with the Medical Monitor:

- Brain metastases have been treated locally and are clinically stable for at least 2 weeks prior to re-initiation of treatment with avelumab
- There are no ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable)
- Patients must be either off steroids or on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent)

In addition, if disease progression is mainly due to a metastatic lesion (nodal or visceral) which in the opinion of the Investigator may be surgically removed or treated with palliative radiation therapy, patients may continue avelumab treatment after the local treatment of such a lesion provided that:

- It has been at least 2 weeks (post minor surgery) or 4 weeks (post major surgery) and the patient has fully recovered from the surgery
- It has been at least 2 weeks since the patient's last dose of radiation therapy and any toxicity related to the radiation therapy is recovered to <Grade 2

The decision to continue treatment should be discussed with the Medical Monitor and documented in the trial records.

A radiographic assessment should be performed after 4-6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment with avelumab.

If the Investigator feels that the patient continues to achieve clinical benefit by continuing treatment, the patient should remain on the trial and continue to receive monitoring according to the Schedules of Assessments (Section 7).

Patients receiving avelumab who experience a CR should strive to be treated for a minimum of 12 months based on clinical judgement of benefit and/or until disease progression or unacceptable toxicity, after confirmation of response. In case a patient with a confirmed CR relapses after stopping treatment during long-term follow-up, but prior to the End of the Trial, 1 re-initiation of treatment is allowed at the discretion of the Investigator and agreement of the Medical Monitor. To be eligible for re-treatment, the patient must not have experienced any toxicity that led to treatment discontinuation. Patients who re-initiate treatment will stay on trial and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedules of Assessments (Section 7.1). Patients who re-initiate treatment will not have to undergo a second screening visit.

CCI [redacted] in Part 2, mandatory pretreatment and during treatment biopsies will be collected as described in Section 7.3.11.

3.2. Part 1 Safety Run-in Cohort: Study Design

The Safety Run-in Cohort (Dose Level 1) will begin by treating 6 patients. The precise starting dose for Hu5F9-G4 will be a priming dose of 1 mg/kg in Week 1 followed by 30 mg/kg weekly for 4 doses. Starting in Cycle 2, 30 mg/kg of Hu5F9-G4 will be given every 2 weeks. This Hu5F9-G4 dose will be combined with the full single-agent dose of 800 mg of avelumab given once every 2 weeks (Table 3-1). The first patient in this cohort will be treated for 14 days prior to enrolling additional patients. After the first 6 patients evaluable for DLT assessment have safely completed the Cycle 1 DLT evaluation period, and if no more than 1 DLT occurs, the cohort will be deemed to be safe by the Clinical Trial Steering Committee (CTSC; Section 11.3). Dose Level 2 will begin by treating 6 patients with the Hu5F9-G4 priming dose of 1 mg/kg in Week 1, followed by 45 mg/kg on Days 8,11,15, 22 and

29 for Cycle 1, continuing weekly in Cycle 2 on Days 1, 8, 15 and 22. Starting in Cycle 3, 45 mg/kg of Hu5F9-G4 will be given every 2 weeks. This Hu5F9-G4 dose will be combined with the full single-agent avelumab dose of 800 mg given every 2 weeks (Table 3-1). The first patient in each cohort will be treated for 14 days before additional patients are enrolled. After the first 6 patients evaluable for DLT assessment have safely completed the Cycle 1 DLT evaluation period, the Clinical Trial Steering Committee (CTSC; Section 11.3) will again meet to determine the Part 2 dose.

The recommended dose for patients in the Expansion Cohort must have a DLT rate less than 33% in at least 6 evaluable patients, and the final dose selection for Part 2 will be made by the CTSC after all available clinical, CCI and PK data are reviewed. Up to an additional 6 evaluable patients may be enrolled to further evaluate safety and PK. The Part 1 dose levels are described in Table 3-1.
Dose evaluation decisions will be made by the CTSC, and DLTs for the combination regimen will be monitored from administration of the priming dose on Day 1 to the end of Cycle 1 (Day 35). The first cycle will be 5 weeks in duration; subsequent cycles will last 4 weeks. Initial tumor response assessments will be performed at Cycle 3 and then after every 8 weeks of treatment (every 2 cycles). CCI Additional assessments to evaluate pseudoprogression or to confirm objective responses, as required by irRECIST (Bohnsack 2014), may also be implemented.

The CTSC may designate additional lower or higher dose levels to explore beyond those described in Table 3-1 after reviewing all available clinical data.

Table 3-1. Part 1 Hu5F9-G4 and Avelumab Dose Levels and Schedule

Dose Cohort	Drug/Dose (Intravenous)	Dose Schedule		
		Cycle 1 (35 days)	Cycle 2 (28 days)	Cycle 3+ (28 days)
1	Hu5F9-G4 — 1 mg/kg (priming dose) *Over 3 hours (± 30 minutes)*	Day 1	—	—
	Hu5F9-G4 — 30 mg/kg *Over 2 hours (± 30 minutes)* *Infusion should begin at least 1 hour after completion of the avelumab infusion (on days when both are administered)*	Days 8, 15, 22, 29	Days 1 and 15	Days 1 and 15
	Avelumab — 800 mg Q2W *Over 1 hour (-10 to +20 minutes)*	Days 8 and 22	Days 1 and 15	Days 1 and 15
2	Hu5F9-G4 — 1 mg/kg (priming dose) Over 3 hours (± 30 minutes)	Day 1	—	—
	Hu5F9-G4 — 45 mg/kg Over 2 hours (± 30 minutes) *Infusion should begin at least 1 hour after completion of the avelumab infusion (on days when both are administered)*	Days 8, 11, 15, 22, 29	Days 1, 8, 15, 22	Days 1 and 15
	Avelumab — 800 mg Q2W Over 1 hour (-10 to +20 minutes)	Days 8 and 22	Days 1 and 15	Days 1 and 15
The following lower dose cohort may be used if ≥2 of 6 patients in Dose Level 1 experience DLTs:				
-1	Hu5F9-G4 — 1 mg/kg (priming dose) Over 3 hours (± 30 minutes)	Day 1	—	—
	Hu5F9-G4 — 20 mg/kg [a] Over 2 hours (± 30 minutes) *Infusion should begin at least 1 hour after completion of the avelumab infusion (on days when both are administered)*	Days 8, 15, 22, 29	Days 1 and 15	Days 1 and 15
	Avelumab — 800 mg Q2W Over 1 hour (-10 to +20 minutes)	Days 8 and 22	Days 1 and 15	Days 1 and 15
The following lower dose cohort may be used if ≥2 of 6 patients in Dose Level 2 experience DLTs:				

Dose Cohort	Drug/Dose (Intravenous)	Dose Schedule		
		Cycle 1 (35 days)	Cycle 2 (28 days)	Cycle 3+ (28 days)
-2	Hu5F9-G4 — 1 mg/kg (priming dose) Over 3 hours (± 30 minutes)	Day 1	—	—
	Hu5F9-G4 — 30 mg/kg [a] Over 2 hours (± 30 minutes) *Infusion should begin at least 1 hour after completion of the avelumab infusion (on days when both are administered)*	Days 8, 11, 15, 22, 29	Days 1, 8, 15, 22	Days 1 and 15
	Avelumab — 800 mg Q2W Over 1 hour (-10 to +20 minutes)	Days 8 and 22	Days 1 and 15	Days 1 and 15

Abbreviations: DLT = dose-limiting toxicity; Q2W = once every 2 weeks.
a. If additional dose reductions are required but the patient is deemed to be benefitting from treatment, the dose of Hu5F9-G4 may be reduced by an additional 50%.

3.2.1. Dose-Limiting Toxicity Assessment

Dosing decisions will be made by the CTSC based on the first 5 weeks of treatment for each patient, referred to as the "Dose-Limiting Toxicity (DLT) Assessment Period."

3.2.1.1. Definition of DLT-evaluable Patients

Patients in the Safety Run-in Cohort in Part 1 are considered evaluable for DLT assessment if they meet either of the following criteria during the DLT assessment period:

- The patient experiences a DLT at any time after initiation of the first infusion of Hu5F9-G4 or any infusion of avelumab.
- The patient completes the minimum safety evaluations (hematology, chemistry, and clinical assessments) after the administration of the study drug combination during the DLT observation period and receives at least 4 complete infusions of Hu5F9-G4 and 2 complete infusions of avelumab, unless a DLT is observed earlier.

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

3.2.1.2. Definition of Dose-limiting Toxicity

All toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE; Appendix C).

DLT Definition: A DLT is defined as any Grade 3 or greater AE that is assessed as related to at least 1 study treatment that occurs during the 5-week DLT Assessment Period (DLT exceptions are defined below). Additionally, any treatment-emergent adverse event (TEAE) that is, in the opinion of the CTSC, of potential clinical significance such that further dosing would expose patients to unacceptable risk, will be considered a DLT.

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

- Grade 3 anemia; however, any Grade 3 hemolytic anemia 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.

  However any occurrence of liver toxicity, as defined by Hy's Law below, is considered a DLT:
  - The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST, and
  - Total Bilirubin >2×ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), and
  - No other reason can be found to explain the combination of increased ALT/AST and total bilirubin.

- Transient Grade 3 nausea, vomiting, diarrhea, local reactions, influenza-like symptoms, myalgias, fever, headache, acute pain, or skin toxicity that resolves to ≤Grade 2 within ≤72 hours after medical management (e.g., supportive care, including immunosuppressant treatment) has been initiated.
- Grade 3 fatigue that resolves to ≤Grade 2 within 1 week on study.
- Grade 3 Hu5F9-G4 or avelumab-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, etc.) that resolves to ≤Grade 2 or baseline within 1 week.
- Grade 3 lipase and/or amylase elevation without clinical or radiological evidence of pancreatitis.
- Grade 3 or 4 lymphopenia or leukopenia not associated with other clinically significant consequences.
- Grade 3 diarrhea or skin toxicity that resolves to Grade ≤1 in less than 7 days after medical management (e.g., immunosuppressant treatment) has been initiated.
- Transient (≤48 hours) Grade 3 fatigue, local reactions, flu-like symptoms, fever, headache, nausea, emesis, and diarrhea.
- Other single laboratory values out of normal range that have no clinical correlate, and resolve to Grade ≤1 or to baseline within 7 days with adequate medical management.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.

3.3. Part 2 Expansion: Study Design

Once the Part 1 Safety Run-in Cohort of the trial is completed and the recommended expansion dose(s) is determined, the CTSC will open Part 2 of the study. Part 2 of the study will treat up to 20 patients with ovarian cancer at the recommended

dose(s) to confirm safety, PK, CCI [redacted] and to document preliminary efficacy in this population.

In Part 2, patients may be enrolled simultaneously without an observation period after the first patient starts treatment. Based on review of ongoing dosing data, the CTSC may recommend testing of multiple doses in Part 2.

Mandatory tumor biopsies will be collected, where medically feasible, from all patients during the Screening Period prior to first dose and at Cycle 3, Day 1 (± 2 weeks). CCI [redacted]
Efficacy will be evaluated using RECIST v1.1 (primary endpoint; Eisenhauer 2009) and irRECIST (secondary endpoint; Bohnsack 2014). Study treatment with study drug may be continued until an unacceptable drug-related toxicity occurs or until disease progression according to irRECIST. Patients who experience initial PD may remain on study until they are deemed to have confirmed progressive disease according to irRECIST, provided all of the following conditions 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, CNS metastases)

Patients who discontinue from treatment for reasons other than confirmed PD will undergo scheduled tumor assessments until documentation of PD or initiation of a new line of anti-cancer therapy, whichever occurs first.

3.4. Number of Sites

Approximately 5 to 8 sites located in the US will participate in this trial. Additional sites may be included based on enrollment and study timelines.

3.5. Estimated Study Duration

It is anticipated that this study will take approximately 20 months to complete.

Patient participation will include Screening, Treatment, and Follow-Up. Screening will last up to 30 days before first dose of study drug, during which time the patient's eligibility and baseline characteristics will be determined. Treatment with study drug may be continued until an unacceptable drug-related toxicity occurs or until disease progression. After treatment, patients will be observed for survival for up to 5 years from date of enrollment, or until death, withdrawal of consent, or the end of the study, whichever occurs first. Patients who discontinue from treatment for reasons other than confirmed PD will undergo scheduled tumor assessments until documentation of PD or initiation of a new line of anti-cancer therapy, whichever occurs first.

Final study analysis may be implemented at the discretion of the CTSC once all Part 2 patients enrolled have come off study or have had at least 1 tumor efficacy assessment to allow for timely reporting of study results. Treatment or long-term follow-up (LTFU) and Survival Follow-up will continue and be reported in an addendum to the Clinical Study Report.

4. PATIENT SELECTION AND ENROLLMENT

Only individuals who fulfill all inclusion criteria and none of the exclusion criteria may be enrolled into the trial, with no exceptions. The Investigator will ensure that the patient or the patient's legal representative has provided written informed consent (in accordance with the procedure described in Section 12.4) before performing any trial assessments that are not part of the patient's routine medical care.

4.1. Inclusion Criteria

1. Meets the criteria for the appropriate cohort:
    - Part 1 Safety Run-in Cohort: Pathologically confirmed advanced solid tumors for which no further conventional therapy is suitable for the patient and for which there is no curative therapy available. Prior checkpoint inhibitor treatment therapy is permitted.
    - Part 2 Ovarian Cancer Expansion Cohort: Histologically or cytologically confirmed, epithelial ovarian, fallopian tube, or peritoneal

cancer patients who are checkpoint inhibitor-naïve. All histological subtypes of ovarian epithelial tumors are allowed. Patients must have had, at any point, documented PD as determined by Gynecologic Cancer InterGroup (GCIG) criteria (Rustin 2011) within 1-6 months after the last day of receiving the last platinum-containing chemotherapy. Patients must have received at least 1 prior line of a platinum-based chemotherapy regimen to be eligible. Patients may have received any additional number of prior systemic therapies for metastatic disease including PARP inhibitors.

2. Part 2 Ovarian Cancer Expansion Cohort: Disease must be measurable or assessable for response according to RECIST v1.1 (primary endpoint; Eisenhauer 2009) and irRECIST (secondary endpoint; Bohnsack 2014).
3. Age ≥18 years.
4. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 2 (Appendix D).
5. Laboratory measurements, blood counts:
    - Hemoglobin ≥9.5 g/dL (RBC transfusions are permitted during the Screening Period and prior to enrollment to meet the hemoglobin inclusion criterion.)
    - Absolute neutrophil count (ANC) ≥1.5 × 10^9/L.
    - Platelets ≥100 × 10^9/L.
6. Laboratory measurements, hepatic function:
    - AST/ ALT ≤3 × upper limit of normal (ULN), or ≤5 × ULN for patients with intrahepatic liver metastases.
    - Bilirubin ≤1.5 × 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. For patients in Part 1 CCI [redacted] a formalin-fixed paraffin-embedded (FFPE) block containing tumor tissue not older than 6 months from the time of screening or a minimum of 10 (preferably 25) unstained tumor slides (cut within 1 week) suitable for PD-L1 expression assessment will be collected. The tissue should be collected from a non-irradiated area and there should be at least 1 measurable lesion remaining for tumor response assessment.
9. Negative urine or serum pregnancy test within 30 days before enrollment and within 72 hours before the first administration of study drug for female patients of childbearing potential.
10. Female patients of childbearing potential must be willing to use 1 highly effective method of contraception during the study and continue for 4 months after the last dose of Hu5F9-G4 and 1 month after the last dose of avelumab (Section 4.6.1).
11. Male patients who are sexually active with a woman of childbearing potential and who have not had vasectomies must be willing to use a highly effective barrier method of contraception during the study and for 4 months after the last dose of Hu5F9-G4 and 1 month after the last dose of avelumab (Section 4.6.2).
12. Patient has provided informed consent.
13. Must be willing and able to comply with the clinic visits and procedures outlined in the study protocol.
14. For Part 2 (Ovarian Cancer Expansion Cohort) only: Willing to consent to 1 mandatory pre-treatment and 1 during-treatment tumor biopsy unless not medically feasible as determined 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 symptomatic or untreated CNS metastases. (Patients with stable, asymptomatic, treated CNS lesions who are off of corticosteroids and radiation therapy for at least 3 weeks are permitted.)
2. Prior or concurrent 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.
   The following are not criteria for exclusion:
   - Localized non-CNS radiotherapy (>14 days before enrollment)
   - Previous hormonal therapy with luteinizing-hormone releasing hormone (LHRH) agonists for prostate cancer
   - Low dose steroids (oral prednisone or equivalent ≤10 mg per day)
   - Treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors
3. For Part 2 Ovarian Cancer Expansion Cohort only: Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab, tremelimumab, or any other antibody or drug specifically targeting T-cell co-regulatory proteins).
4. Prior treatment with CD47 or SIRPα targeting agents.
5. Known active or chronic hepatitis B or C infection or human immunodeficiency virus (HIV).
6. RBC transfusion dependence, defined as requiring more than 2 units of RBCs transfused during the 4-week period prior to Screening. RBC transfusions are permitted during the Screening Period and prior to enrollment to meet the hemoglobin inclusion criteria.
7. Prior organ transplantation, including allogeneic stem-cell transplantation, requiring immunosuppression.

8. Prior hemolytic anemia or Evans Syndrome in the last 3 months.
9. Hypersensitivity to the active substance or to any of the other excipients of Hu5F9-G4 or avelumab, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.03, Grade ≥3; Appendix C).
10. Significant medical diseases or conditions that would substantially worsen 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, significant acute or chronic infections, severely immunocompromised state, and congestive heart failure (New York Heart Association (NYHA) Class II-IV).
11. Known history of inflammatory colitis, inflammatory bowel disease, pneumonitis, or pulmonary fibrosis.
12. History of uncontrolled intercurrent illness including but not limited to:
    - Hypertension uncontrolled by standard therapies (not stabilized to 150/90 mmHg or lower)
    - Uncontrolled active infection
    - Uncontrolled diabetes (e.g., hemoglobin A1c ≥8%)
    - Uncontrolled asthma
13. Radiotherapy within 14 days prior to enrollment.
14. For Part 2 Expansion Cohort only: Previous malignant disease (other than the tumor disease for this trial and with the exception of adequately treated non-melanoma skin cancers, and carcinoma in situ of skin, bladder, cervix, colon/rectum, or breast) unless in a stable remission for at least 2 years prior to study entry.
15. History of psychiatric illness or substance abuse likely to interfere with ability to comply with protocol requirements or give informed consent.
16. Patient or designees are or become incapable of providing legal informed consent.

17. Current use of the following medications at the time of enrollment:
    - Immunotherapy or immunosuppressive drugs (e.g., chemotherapy or systemic corticosteroids) EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent; c. steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
    - Growth factors (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor) EXCEPT for erythropoietin and darbepoetin alpha.
    - Herbal remedies with immunostimulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (e.g., hypericin).
18. Administration of a live vaccine within 28 days prior to enrollment.
19. Pregnancy or active breast feeding.
20. Active autoimmune disease or treatment with systemic immunosuppression for organ transplantation.

    The following are not criteria for exclusion:
    - Type I diabetes mellitus
    - Vitiligo
    - Mild-to-moderate psoriasis
    - Clinically stable hypo- or hyperthyroid disease not requiring immunosuppressive treatment
21. 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, will receive a unique patient 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.

Screening laboratory assessments may be tested repeatedly within the 30 days prior to the first dose of study treatment. Patients who initially failed screening may repeat the screening process if the patient's medical condition has changed.

All patients who provide informed consent must be registered in the Interactive Response Technology (IRT) system, including any screen failures.

A patient is defined as enrolled in the study once all eligibility criteria have been satisfied and the patient is assigned to a cohort or study arm assignment. After signing the informed consent, eligible patients are expected to receive the first dose of Hu5F9-G4 (Cycle 1, 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 (IRB)/Research Ethics Committee (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 patient number at the time of consent. The site will register the patient through IRT.

Prior to being assigned to a dose cohort or treatment arm, patients must have signed the ICF and satisfied all of the study eligibility criteria. The Investigator will

determine the eligibility of the patient. Once patients have been assigned to a dose cohort or treatment arm, they will be considered enrolled.

4.6. Contraception Requirements

4.6.1. Female Patients

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 forms of contraception (defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly):

- Bilateral tubal occlusion
- Vasectomized partner
- Intra-uterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- 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), spermicides only, and lactational amenorrhea method. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Contraception must be effective at the first administration of any of the study drugs (Hu5F9-G4 or avelumab), throughout the trial, and for 4 months after the last dose of Hu5F9-G4 or 1 month after the last dose of avelumab, whichever occurs latest.

4.6.2. Male Patients

A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a highly effective barrier method of birth control (e.g., either 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, and all men must also agree not donate sperm for the duration of the study treatment and for 4 months after the last dose of Hu5F9-G4 or 1 month after the last dose of avelumab, whichever occurs latest.

Contraception must be effective at the first administration of any of the study drugs (Hu5F9-G4 or avelumab), throughout the trial, and for 4 months after the last dose of Hu5F9-G4 or 1 month after the last dose of avelumab, whichever occurs latest.

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

5. STUDY DRUG INFORMATION

Refer to the Pharmacy Manual for detailed instructions for Hu5F9-G4 and avelumab preparation and handling.

5.1. Physical Description of Study Drug

5.1.1. Hu5F9-G4

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 IV infusion.

Hu5F9-G4 active 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.

5.1.2. Avelumab

Avelumab (BAVENCIO®) is a programmed death ligand-1 (PD-L1) blocking antibody. Avelumab is a human IgG1 lambda monoclonal antibody that has a molecular weight of approximately 147 kDa.

BAVENCIO (avelumab) Injection for intravenous use is a sterile, clear, colorless to slightly yellow concentrate for solution for infusion. It is presented at a concentration of 20 mg/mL in single-use glass vials closed with a rubber stopper and sealed with an aluminum polypropylene flip-off seal. Each single-dose vial contains 200 mg avelumab in 10 mL (20 mg/mL). Each mL contains 20 mg avelumab, D-mannitol (51 mg), glacial acetic acid (0.6 mg), polysorbate 20 (0.5 mg), sodium hydroxide (0.3 mg), and Water for Injection. The pH range of the solution is 5.0 to 5.6.
The labeling complies with the requirements of the applicable regulatory agencies.
Additional details about avelumab are provided in Appendix B.

6. TREATMENT ADMINISTRATION

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

6.1.1. Dosing

The Hu5F9-G4 and avelumab dose levels and schedules are outlined above in Table 3-1 for Part 1, and also in the Study Schemas for Part 1 and Part 2. The dose of Hu5F9-G4 will be calculated based on the weight of the patient measured within 72 hours prior to enrollment 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 6.4. Dose modifications for changes in body weight <10% may be made according to local institutional guidelines.

Avelumab will be given at a fixed dose of 800 mg every 2 weeks for all patients.

6.1.2. Premedication

Hu5F9-G4

Premedication with oral acetaminophen 650–1000 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). If less than 4 hours has elapsed since a prior dose of acetaminophen has been given, for example, as a premedication for avelumab, the dose of acetaminophen premedication for Hu5F9-G4 may be omitted. 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 Section 6.5.1.1.

Avelumab

Premedication with an antihistamine and with acetaminophen (for example, 25 to 50 mg intravenous or oral diphenhydramine and 500 to 650 mg oral acetaminophen) approximately 30 to 60 minutes prior to the first 4 doses of avelumab is mandatory. Premedication should be administered for subsequent avelumab doses based on clinical judgment and presence/severity of prior infusion-related reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate. However, the prophylactic use of systemic corticosteroids is not permitted.

6.1.3. Timing of Dosing

In both study parts, Cycle 1 will be 5 weeks in duration and Cycles 2+ will be 4 weeks. The Hu5F9-G4 and avelumab dose levels and schedules are outlined above in Table 3-1, and in the Study Schemas provided above for Part 1 and Part 2.

On days when both study drugs are being administered, Hu5F9-G4 will be administered at least 1–2 hours after the completion of avelumab infusion.

6.1.4. Patient Monitoring After Infusion

Following the first 4 avelumab infusions, patients must be observed for 1 hour after the completion of the infusion for potential infusion-related reactions.

All patients should be monitored for 1 hour after the completion of each Hu5F9-G4 weekly infusion for the first 5 weeks. Post-infusion monitoring should begin after Hu5F9-G4 is given. Post-infusion monitoring is not required for doses after Cycle 1. Patients who experience any study drug-related AEs during the observation period should be further monitored, as clinically appropriate.

Immediate access to an Intensive Care Unit (ICU) or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen) must be available for use in the treatment of infusion-related reactions. Infusion of avelumab will be stopped if the patient experiences Grade ≥2 infusion-related, allergic, or anaphylactoid reactions.

6.1.5. 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 twice weekly dosing schedule.
- Patients who experience an interruption of >4 weeks after receiving at least 1 dose (i.e., 30 mg/kg, 45 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 twice weekly dosing schedule.

- Avelumab must be administered as regularly scheduled (e.g. Hu5F9-G4 repriming doses may be administered on the same day as avelumab is given and administration of avelumab every 2 weeks 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):

- 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

6.2. Hu5F9-G4 Preparation and Administration

6.2.1. Preparation

Patients should be premedicated in accordance with Section 6.1.2. Hu5F9-G4 should be prepared as outlined in the Pharmacy Manual.

6.2.2. Administration

6.2.2.1. Priming Dose

All patients will receive a priming dose of 1 mg/kg Hu5F9-G4 on Day 1 of Cycle 1. The duration of the infusion of the priming dose will be 3 hours (±30 minutes). The priming dose will be administered in Cycle 1 only. Repriming doses are required for patients who experience dose interruptions or treatment delays of >4 weeks. Details are provided in Section 6.4.2.3.

6.2.2.2. Maintenance Dose

The priming dose of Hu5F9-G4 will be followed by the maintenance doses of Hu5F9-G4.

In Part 1 of the study, 2 doses and 2 dosing schedules are planned. Additional dose levels and schedules may be evaluated based on emerging study data and after CTSC review.

In Dose Level 1, Hu5F9-G4 maintenance doses will be administered at a dose of 30 mg/kg as an IV infusion over 2 hours (±30 minutes) Cycle 1 doses will be administered on Days 8, 15, 22, and 29, while doses in Cycles 2+ will be administered on Days 1 and 15.

In Dose Cohort 2, Hu5F9-G4 will be administered at a dose of 45 mg/kg as an IV infusion over 2 hours (±30 minutes). Cycle 1 doses will be administered on Days 8, 11, 15, 22, and 29. Cycle 2 doses will be administered on Days 1, 8, 15, and 22. Doses in Cycles 3+ will be administered on Days 1 and 15.

In Part 2 of the study, Hu5F9-G4 will be dosed based on the dose and schedule selection that will be made by the CTSC after all available clinical, CCI and PK data are reviewed from Part 1.

On days when both study drugs are given, Hu5F9-G4 will be administered at least 1 hour after the completion of the avelumab infusion. Proposed doses of study drug

to be administered are outlined above in Table 3-1, and in the Study Design Schemas provided above for Part 1 and Part 2.

Modifications to the infusion rate due to infusion-related reactions are described in Section 6.5.2. Patients will receive Hu5F9-G4 Q2W until the criteria in Section 8 are met.

6.3. Avelumab Preparation and Administration

6.3.1. Preparation

Patients should be premedicated in accordance with Section 6.1.2. Avelumab should be prepared as outlined in the Pharmacy Manual.

6.3.2. Administration

No priming dose is required for avelumab. In Part 1 of the study, avelumab will be administered intravenously at a fixed dose of 800 mg over 1 hour (-10 to +20 minutes). Because of the different cycle lengths (due to the priming dose of Hu5F9-G4) Cycle 1 doses will be administered on Days 8 and 22, while doses in Cycles 2+ will be administered on Days 1 and 15. Administration should be through an IV line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micron). Drugs should not be co-administered through the same IV line. In Part 2 of the study avelumab will be fixed at 800 mg.

On days when both study drugs are given, Hu5F9-G4 will be administered at least 1 hour after the completion of the avelumab infusion. Proposed doses of study drug to be administered are outlined above in Table 3-1, and in the Study Schemas provided for Part 1 and Part 2.

Modifications to the infusion rate due to infusion-related reactions are described in Section 6.5.2. Patients will receive avelumab once every 2 weeks until the criteria in Section 8 are met.

6.4. Dose Delays, Dose Modifications, and Treatment Termination

6.4.1. Treatment Termination: Hu5F9-G4 and Avelumab

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 irRECIST (irPD; Bohnsack 2014) may not be indicative of true PD. Patients who meet criteria for unconfirmed irPD while receiving treatment will be permitted to continue treatment if they meet all of the criteria provided in Section 3.1. 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 avelumab alone, the patient may continue to participate in the study provided that other protocol stipulations are met.

Treatment termination is defined as permanent discontinuation of both study drugs.

6.4.2. Hu5F9-G4

6.4.2.1. Dose Modifications: Study Part 1

Proposed doses of study drug to be administered are outlined above in Table 3-1. Dose modifications or dose delays should be implemented for any AEs that meet the DLT criteria, as defined in Section 3.2.1.2 (refer to Part 1 in Table 6-1). Hu5F9-G4 may be re-introduced at a lower dose level if the AE has recovered to Grade 0-1, or to baseline, within 4 weeks. Data from patients who restart dosing after the recovery period will not contribute to the MTD evaluation at the lower dose level. Treatment delays of more than 4 weeks (such as for an unrelated medical condition with expected recovery) must be approved by the CTSC. 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, 45 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 twice-weekly dosing schedule (Section 6.1.5, Repriming).

6.4.2.2. Dose Modifications: Study Part 2

Patients who experience a Grade 3 or 4 study drug-related AE (that matches the criteria for a DLT, as defined in Part 1) should have their Hu5F9-G4 doses reduced in subsequent treatments to the next lower dose level, or as suggested in discussion with the Medical Monitor. Table 6-1 outlines the toxicities requiring an Hu5F9-G4 dose reduction. If the Grade 3 or 4 AE recurs after dose reduction, study drug should be discontinued, unless the treating physician and Sponsor agree that the patient is clinically benefitting. If additional dose reductions are required but the patient is deemed to be benefitting from treatment, the dose of Hu5F9-G4 may be reduced by an additional 50%. Refer to Table 3-1 for dose modification level -1, that should be made based on the proposed initial assigned dose of Hu5F9-G4 [Dose Level 1] in Part 2.)

Table 6-1. Hu5F9-G4-related Toxicities Requiring Dose Reduction

Toxicity	Specific Finding Requiring Action	Recommended Action Taken with Hu5F9-G4
DLT in Study Part 1	A DLT is defined as: any Grade 3 or greater AE assessed as related to study treatment during the 5-week DLT assessment period (refer to exceptions listed in Section 3.2.1.2).	Actions taken for DLTs observed in Part 1 should be in accordance with Section 3.2 and Section 6.4.2.1.
Any AE assessed as related to Hu5F9-G4	Grade 3 or greater	• First occurrence: reduce by 1 dose level. • If recurs after 1 dose level reduction: permanently discontinue unless patient is clinically benefitting. • Second occurrence: second dose level reduction. • After 2 dose level reductions: permanently discontinue.
Anemia	Grade 3 hemolytic anemia that is medically	• First occurrence: Reduce by 1 dose level.

Toxicity	Specific Finding Requiring Action	Recommended Action Taken with Hu5F9-G4
	significant (requiring hospitalization or prolongation of existing hospitalization, disabling, or limiting self-care ADLs)	• If recurs after 1 dose level reduction: permanently discontinue unless patient is clinically benefitting. • Second occurrence: second dose level reduction. • After 2 dose level reductions: permanently discontinue.
	Grade 4	First occurrence: permanently discontinue unless patient is clinically benefitting.
Hyperbilirubinemia	Grade 3 indirect/ unconjugated hyperbilirubinemia that does not resolve to ≤Grade 2 with supportive care within 1 week and is associated with other clinically significant consequences	• First occurrence: reduce by 1 dose level. • If recurs after 1 dose level reduction: permanently discontinue unless patient is clinically benefitting. • Second occurrence: second dose level reduction. • After 2 dose level reductions: permanently discontinue.
	Grade 4	First occurrence: permanently discontinue unless patient is clinically benefitting.
Electrolytes	Grade 3 isolated abnormality that does not resolve to ≤Grade 2 with supportive care within 1 week and is associated with other clinically significant consequences	• First occurrence: reduce by 1 dose level. • If recurs after 1 dose level reduction: permanently discontinue unless patient is clinically benefitting. • Second occurrence: second dose level reduction. • After 2 dose level reductions: permanently discontinue.
	Grade 4	First occurrence: permanently discontinue unless patient is clinically benefitting.
ALT, AST, or alkaline phosphatase	Grade 3 elevation that does not resolve to ≤Grade 2 with supportive care within 1 week and is associated with other clinically significant consequences	• First occurrence: reduce by 1 dose level. • If recurs after 1 dose level reduction: permanently discontinue unless patient is clinically benefitting. • Second occurrence: second dose level reduction. • After 2 dose level reductions:

Toxicity	Specific Finding Requiring Action	Recommended Action Taken with Hu5F9-G4
		permanently discontinue.
	If the finding is consistent with the definition of Hy's Law (Section 3.2.1.2)	Permanently discontinue treatment.
	Grade 4	First occurrence: permanently discontinue unless patient is clinically benefitting.
Nausea, vomiting, or diarrhea	Grade 3 that does not resolve to ≤Grade 2 with supportive care within 72 hours	• First occurrence: reduce by 1 dose level. • If recurs after 1 dose level reduction: permanently discontinue unless patient is clinically benefitting. • Second occurrence: second dose level reduction. • After 2 dose level reductions: permanently discontinue.
	Grade 4	First occurrence: permanently discontinue unless patient is clinically benefitting.
Fatigue	Grade 3 that does not resolve to ≤Grade 2 with supportive care within 2 weeks on study	• First occurrence: reduce by 1 dose level. • If recurs after 1 dose level reduction: permanently discontinue unless patient is clinically benefitting. • Second occurrence: second dose level reduction. • After 2 dose level reductions: permanently discontinue.
	Grade 4	First occurrence: permanently discontinue unless patient is clinically benefitting.
Hu5F9-G4 infusion-related reactions	Grade 3 in the presence of an optimal pretreatment regimen (defined as acetaminophen or a comparable non-steroidal anti-inflammatory agent, plus an antihistamine and corticosteroids)	• First occurrence: reduce by 1 dose level. • If recurs after 1 dose level reduction: permanently discontinue unless patient is clinically benefitting. • Second occurrence: second dose level reduction. • After 2 dose level reductions: permanently discontinue.
	Grade 4	First occurrence:

Toxicity	Specific Finding Requiring Action	Recommended Action Taken with Hu5F9-G4
		If priming dose, permanently discontinue. For subsequent dose, permanently discontinue unless patient is clinically benefitting.
Tumor lysis or electrolyte disturbances	Grade 3 tumor lysis or electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia, etc.) that does not resolve to ≤Grade 2 or baseline within 1 week	• First occurrence: reduce by 1 dose level. • If recurs after 1 dose level reduction: permanently discontinue unless patient is clinically benefitting. • Second occurrence: second dose level reduction. • After 2 dose level reductions: permanently discontinue.
	Grade 4	First occurrence: permanently discontinue unless patient is clinically benefitting.

Abbreviations: 1st = first; 2nd = second; AE = adverse event; ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DLT = dose-limiting toxicity.

6.4.2.3. Interruption of Hu5F9-G4 Treatment

For patients who experience dose interruptions, instructions for repriming are provided in Section 6.1.5.

6.4.3. Avelumab

6.4.3.1. Dose Modifications

Recommended dose modifications of avelumab for adverse reactions are provided in the Avelumab PI, provided in Appendix B. Detailed information regarding clinical and laboratory monitoring guidelines for early detection of adverse reactions to avelumab and recommended management (immunosuppressant treatment guidelines) are described in the Warnings and Precautions (5) section of the Avelumab PI.

6.5. Safety Management Guidelines

6.5.1. Hu5F9-G4-related Events

6.5.1.1. Management of Infusion-related 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-related 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 consider treating the patient with diphenhydramine 50 mg IV (or equivalent) and/or 500–750 mg oral acetaminophen.
  - Remain at bedside and monitor patient until resolution of symptoms.
  - Corticosteroid therapy may also be given at the discretion of the Investigator.
  - If the infusion is interrupted, wait until symptoms resolve, then restart the infusion at 50% of the original infusion rate.
  - If no further complications occur after 1 hour (± 10 minutes), the rate may be increased to 100% of the original infusion rate. Monitor the patient closely.
  - If symptoms recur, stop infusion and disconnect patient from the infusion apparatus. No further Hu5F9-G4 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-related reaction during the post-infusion observation period that does not resolve during that time should be observed until the AE resolves, with vital sign measurements as medically indicated for the management of the AE.

- For Grade 3 or Grade 4 infusion-related reactions, where Grade 3 is described as prolonged infusion-related reactions (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion), or recurrence of symptoms following initial improvement, or where hospitalization is indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates).

  Grade 4 is described as having life-threatening consequences and where urgent intervention indicated.
  - Immediately discontinue infusion of Hu5F9-G4.
  - Begin an IV infusion of normal saline, and consider treating the patient as follows:

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

recommended for the subsequent 2 doses. Continued premedication with corticosteroids beyond these 2 doses may be administered at the discretion of the treating physician.

- Patients who receive premedication with a corticosteroid and still experience a Grade 3 or 4 infusion-related reaction will be permanently discontinued from study treatment.
- Investigators should follow their institutional guidelines for the treatment of anaphylaxis.
- All patients with Grade 3 or greater 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).

6.5.1.2. 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.

6.5.1.3. Hemagglutination and Microangiopathy

In the Phase 1 trial experience with Hu5F9-G4 in solid tumors and AML, agglutination of RBCs has been observed on peripheral smear. Hu5F9-G4-related microangiopathy is a possible sequela of hemagglutination; however, it has not been observed in the ongoing Phase 1 clinical trials to date. In addition, AEs may be associated with findings of hemagglutination. Monitoring of hemagglutination and microangiopathy includes physical exam assessments, complete blood counts (CBCs), peripheral smears, serum chemistries, and D-dimer testing as outlined in the schedule of assessments (SOA). Peripheral smears will be read by local sites with reporting of RBC agglutination, spherocytosis, and evidence of RBC destruction

(e.g., schistocytosis, fragments) when present. The presence or absence of hemagglutination and/or microangiopathy on peripheral smear will be incorporated into the AE severity grading for hemagglutination and microangiopathy, as described below. The degree of peripheral smear findings will be quantified according to the appropriate scale (Appendix E) for sites that have the capability to do so, but is not required. CCI [redacted] 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

6.5.1.4. 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 RBC 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 7.3.6.7. 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 Investigator, perform the following procedures:
    - Front Type: EDTA/glycine-acid (EGA) Treat cells ×2 (maximum) and Warm Wash ×4 (minimum) with 0.9% Saline.
    - Back Type: Perform reverse anti-human globulin for both A and B.
    - If a valid ABO type cannot be obtained, mark the final report as invalid and notify the transfusion service for the site.
2. Antibody screen
   If a pan-agglutinin/warm autoantibody is present in low ionic strength solution (LISS), repeat the antibody screen with polyethylene glycol (PeG). Perform PeG adsorption studies and elution studies.

6.5.1.4.1. Blood Components for Transfusion

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

6.5.2. Avelumab-related Events

Detailed safety management guidelines are provided in the Avelumab PI, (Appendix B) for the safety issues listed below:

- Immune-mediated reactions
  - Pneumonitis
  - Immune-mediated hepatitis
  - Immune-mediated colitis
  - Immune-mediated endocrinopathies
    - Adrenal insufficiency
    - Thyroid disorders (Hypothyroidism/Hyperthyroidism)
    - Type 1 diabetes mellitus
  - Immune-mediated nephritis and renal dysfunction
- Other immune-related adverse reactions
- Infusion-related reactions
- Embryo-fetal toxicity

To mitigate infusion-related reactions, patients have to be premedicated with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of

avelumab (Section 6.1.2). Premedication should be administered for subsequent avelumab doses based on clinical judgment and presence/severity of prior infusion-related reactions.

Management of infusion-related reactions should follow guidelines provided in Table 6-2.

Table 6-2. Treatment Modification for Symptoms of Infusion-related Reactions Associated with Avelumab

NCI CTCAE Grade	Treatment Modification for Avelumab
Grade 1: mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2: moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	• Temporarily discontinue avelumab infusion. • Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4: severe or life-threatening • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the avelumab infusion immediately and disconnect infusion tubing from the subject. • Subjects have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.

Source: Merck KGaA.
Abbreviations: IV = intravenous; NCI CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for the next scheduled infusion. If no infusion-related reaction is observed in the next scheduled infusion the infusion rate may be returned to baseline at the all subsequent infusions. If an

infusion-related reaction occurs, all details about drug preparation and infusion must be recorded on the appropriate eCRF.

Patients should be instructed to report any delayed reactions to the Investigator immediately.

Investigators should also monitor patients closely for potential infusion-related AEs (irAEs), which may become manifest at any time during treatment. Such events include but are not limited to pneumonitis, hepatitis, colitis, endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type 1 diabetes mellitus), myocarditis, myositis, rash.

6.5.2.1. Immune-related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, irAEs may occur.
Treatment of irAEs is mainly dependent upon severity (NCI CTCAE grade):

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring
- Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)
- Grade 3 to 4: treat with high dose corticosteroids

Treatment of irAEs should follow guidelines presented in Table 6-3.

Table 6-3. Management of Immune-Related Adverse Events (Avelumab)

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: <4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g., loperamide)	Close monitoring for worsening symptoms Educate patient subject to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline;	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤1: Resume avelumab therapy

IV fluids indicated <24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool		If persists >5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade ≤1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists >3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash (NCI CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If Grade 2 persists >1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: **Treat as Grade 3 to 4.**
Grade 3 to 4 Grade 3: Covering >30% body surface area; Grade 4: Life-threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).
Pulmonary irAEs		
Grade of Pneumonitis (NCI CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1	Consider withholding avelumab	Re-assess at least every 3 weeks

Radiographic changes only	therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening or for recurring Grade 2: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT >ULN to 3.0 x ULN and/or Total bilirubin >ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.
Grade 2 AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days	If returns to Grade ≤1: Resume routine monitoring; resume avelumab therapy. If elevation persists >5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT >5 x ULN and/or total bilirubin >3 x ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent	If returns to Grade ≤1: Taper steroids over at least 1 month If does not improve in >3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily

	Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If no response within an additional 3 to 5 days, consider other immunosuppressants according to local guidelines.
Renal irAEs		
Grade of Creatinine Increased (NCI CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased >ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased >1.5 and ≤6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased >6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤1: Taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g., troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalize. In the presence of life-threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.*	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.

	Consider myocardial biopsy if recommended per cardiology consult.	
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g., azathioprine, cyclosporine A).
*Local guidelines, or e.g., European Society of Cardiology (ESC) or American Heart Association (AHA) Guidelines ESC Guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA Guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		
Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e., hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e., hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

Hypopituitarism/ Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e., subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	Resume avelumab once symptoms and hormone tests improve to Grade ≤1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.
Other irAEs (not described above)		
Grade of other irAEs (NCI CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day	If improves to Grade ≤1: Taper steroids over at least 1 month.

	prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3** irAE lasting 12 weeks or longer	Permanently discontinue avelumab therapy Specialty consult	

Source: Merck KGaA.

Abbreviations: ACTH = adrenocorticotropic hormone; ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = B-type natriuretic peptide; CK-MB = creatine kinase MB; CT = computed tomography; FSH = follicle-stimulating hormone; GH = growth hormone; IGF-1 = insulin-like growth factor 1; irAE = immune related adverse event; IV = intravenous; LH = luteinizing hormone; MRI = magnetic resonance imaging; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PRL = prolactin;T4 = thyroxine; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

6.6. Prohibited Medications

6.6.1. Hu5F9-G4

Anti-cancer therapies (including chemotherapy, hormonal therapy, and investigational agents) are prohibited while patients are on study therapy. However, low dose steroids (oral prednisone or equivalent ≤10 mg per day or equivalent), localized non-CNS radiotherapy, previous hormonal therapy with LHRH agonists for prostate cancer, treatment with bisphosphonates or RANKL inhibitors and other supportive care medicines are allowed during the study.

6.6.2. Avelumab

The following treatments must not be administered during the trial except where unavoidable for the treatment of adverse events:

- Immunotherapy, immunosuppressive drugs (that is, chemotherapy or systemic corticosteroids) except:
    - When required for the treatment of immune-related adverse events or infusion-related reactions/hypersensitivity
    - Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent
    - Systemic corticosteroids for management of patients with allergy to CT IV Radiographic Contrast Media.
- Administration of a live vaccine within 28 days prior to study treatment.
- Growth factors (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor). Exception: Erythropoietin and darbepoietin alpha may be prescribed at the investigator's discretion.
- Herbal remedies with immunostimulating properties (for example, mistletoe extract) or known to potentially interfere with major organ function (for example, hypericin).

The following non-drug therapies must not be administered during the trial:

- Surgery to any tumor lesion for symptom management or tumor control is not permitted during the study treatment. For any other surgical interventions planned during the study, study treatment should be delayed to allow patient's recovery, for up to a maximum of 4 weeks.
- Radiotherapy with the exception of palliative bone-directed radiotherapy.

Palliative short-course, limited-field (i.e., ≤10 fractions and ≤30% bone marrow involvement or per institutional standard) bone-directed radiotherapy may be administered during the trial.

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

Patients who complete, terminate, or decline further treatment should return for their Safety Follow-up Visit 30 days (± 1 week) after their last dose of last study drug received. The Safety Follow-up Visit assessments are described in Section 7.3.16. Patients will receive Safety Follow-up Contact by phone 90 days after their last dose of last study drug received (± 5 days). Patients who develop study drug-related AEs or SAEs within the 90-day period will be seen by the study physician.

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 last study drug received, unless they are experiencing ongoing study drug-related AEs and serious adverse events (SAEs). For patients being followed for ongoing SAEs or study drug-related AEs, follow-up visits will continue at least every 4 weeks until resolution or return to baseline, stabilization of the event, the patient is lost to follow-up or withdraws consent, or the Medical Monitor deems it necessary, whichever occurs first. If a patient begins another anti-cancer therapy, Safety Follow-up Visits will stop.

All patients, including those who discontinue study drug early, will be followed for response until progressive disease (PD) or new anti-cancer therapy and, if feasible, for survival (patients will be contacted every 3 months [± 1 month] from the date of the Safety Follow-up Visit, 5 years from the date that the last patient is enrolled into the study, or full withdrawal of consent) until death or study closure, whichever occurs first. 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, or they withdraw consent.

7. STUDY EVALUATIONS

7.1. Schedules of Assessment for Part 1 and Part 2

Table 7-1 outlines the assessments for Study Parts 1 and 2, Dose Level 1 and Table 7-2 outlines the assessments for Study Parts 1 and 2, Dose Level 2. Unless otherwise noted procedures are to be completed prior to any study drug infusion. Table 7-3 outlines the assessments for follow-up (for Part 1 and Part 2) of the study. Table 7-4 outlines the blood sampling times for PK, CCI and RO.

Table 7-1. Schedule of Assessments (Study Part 1 and Part 2, Dose Level 1)

Cycle	SC	**Priming Cycle 1 (35 days)**							**Cycle 2 (28 days)**		**Cycle 3 (28 days)**		**Cycles 4+ (28 days)**	
Cycle Day	SC	1	2	8	9	15	22	29	1	15	1	15	1	15
Visit Window	-30	None		±1 Day					± 2 Days		± 2 Days		± 2 Days	
Assessments														
Informed Consent	X													
Demographics	X													
Medical and cancer history	X													
Eligibility criteria	X													
Cohort assignment[a]	X													
Physical examination[b,f]	X	X		X		X	X	X	X[b]		X[b]		X[b]	
Vital signs[c]	X	X		X		X	X	X	X	X	X	X	X	
Weight	X	X							X		X		X	
ECG[d]	X	X		X					X					
ECOG performance status[f]	X	X							X		X		X	
Pregnancy test[e,f]	X	X							X		X		X	
Serum chemistry[f]	X	X	X	X		X	X	X	X	X	X	X	X	X
CBC, differential, platelets, reticulocytes[f]	X	X	X	X		X	X	X	X	X	X	X	X	X
Peripheral blood smear[f,g]		X	X	X		X		X	X		X			
Serum uric acid, phosphorous[f]	X	X	X	X		X	X	X						
Haptoglobin, D-dimer, thrombin time, plasma fibrinogen[f]	X		X	X		X	X	X	X		X		X	
PT/INR, aPTT[f]	X			X					X		X		X	
ACTH, FSH, TSH[f]	X			X						X			X[s]	
T3 (Total), T4 (Free)[f]	X			X						X			X[s]	
ABO/Rh, DAT[f,h]	X													
Urinalysis[f]	X					X	X							

Cycle	SC	**Priming Cycle 1 (35 days)**							**Cycle 2 (28 days)**		**Cycle 3 (28 days)**		**Cycles 4+ (28 days)**	
Cycle Day	SC	1	2	8	9	15	22	29	1	15	1	15	1	15
Visit Window	-30	None		±1 Day					± 2 Days		± 2 Days		± 2 Days	
Assessments														
Pharmacokinetics[i]		X	X	X	X		X		X	X	X		Q3 cycles See Table 7-4	
CCI														
Antidrug antibodies[f,l]		X							X		X		Q3 cycles	
Tumor biopsy[m]	X										X			
Tumor markers, if applicable[n]	X[n]								X		X		X[n]	
Response assessment[o]	X[p]										X[q]		Q2C odd cycle[q]	
DLT assessment[r]									X					
Adverse events		→											→	
Concomitant medications		→											→	
Hu5F9-G4 premedication[t]		X		X										
Hu5F9-G4 administration		X[a]		X		X	X	X	X	X	X	X	X	X
Avelumab premedication[t]				X			X		X	X				
Avelumab administration				X			X		X	X	X	X	X	X

Abbreviations: 1st = first; ABO = any of the four blood groups A, B, AB, and O comprising the ABO system; ADAs = anti-drug antibodies; aPTT = activated partial thromboplastin time; CBC = complete blood count; DAT = direct antiglobulin test; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; INR = international normalized ratio; PE = physical examination; PT = prothrombin time; Rh = Rhesus factor; RO = receptor occupancy; SC = screening; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone.

Footnotes:

a. First dose of Hu5F9-G4 (priming dose) must be given within 30 days of consent.
b. Full PE is required at Screening, a symptom-directed PE is acceptable thereafter; height should be recorded during Screening only; weight should be recorded during Screening and on Day 1 of each cycle.
c. Prior to infusion and within 30 minutes after each infusion (if applicable); vital signs should include heart rate, respiratory rate, blood pressure, and temperature. Height should be recorded during Screening only.
d. A single ECG will be performed at Screening. Triplicate ECGs will be performed at the visits indicated after Screening, within 2 hours prior to avelumab infusion if applicable, and within 30 minutes of the end of Hu5F9-G4 infusion; additional guidance is provided in Section 7.3.2.
e. A urine or serum pregnancy test is 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) 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 performed within the 72 hours prior to dosing. After Screening, all pregnancy tests can be urine or serum pregnancy tests and should be performed on Day 1 of every cycle; additional guidance is provided in Section 7.3.5. Contraceptive requirements for female patients are outlined in Section 4.6.1, and for male patients in Section 4.6.2.
f. Pre-infusion assessments may be performed up to 72 hours before study drug treatment. Most laboratory assessments will be performed locally at each study center's laboratory by means of their established methods; analytes to be assessed by the local laboratory or specialty laboratories are presented in Table 7-5.
g. Peripheral blood smear slides from Cycle 1 will be retained and sent to the Sponsor for storage. Collection guidelines are provided in Section 7.3.6.3. Peripheral blood smears are also to be collected 1 hour (± 30 minutes) after completion of any blood transfusion.
h. Type and screen; additional guidance is provided in Section 7.3.6.7 and Table 7-5.
i. Refer to Table 7-4 for PK time point details; samples should be drawn on the contralateral arm from where the study drugs are being infused and they should not be drawn from central lines where the relevant study drugs have been previously infused; additional guidance is provided in Section 7.3.8.
[redacted]
k. Not applicable.
l. ADAs to Hu5F9-G4 [redacted] should be assessed on Day 1 of Cycles 1, 2, 3, and 4 and then every 3 cycles until Cycle 13, at the End of Treatment Visit, and at the 30-day Safety Follow-up Visit. Additional guidance is provided in Section 7.3.10.
m. Biopsies are to be collected during the Screening Period prior to first dose and on Cycle 3 Day 1 (± 2 weeks); tumor biopsies are [redacted] mandatory for Part 2 where medically feasible. [redacted]
n. Tumor markers should be obtained at Screening. If applicable, they should also be obtained on Day 1 of Cycles 2, 3, and 4. From Cycle 5 and onward, they may be obtained every 2 cycles; additional guidance is provided in Section 7.3.12.
o. After Cycle 3, the adjustment window is ± 2 weeks to coordinate with treatment cycles; additional guidance is provided in Section 7.3.12.
p. Historic imaging may be used for Screening diagnostic imaging if performed within 30 days of the first dose of Hu5F9-G4; additional guidance is provided in Section 7.3.12.

Footnotes:

q. Efficacy assessment should be conducted at ± 1 week of the Cycle 3 Day 1 visit, and then at ± 2 weeks of the Day 1 visit of every other subsequent cycle (i.e., Day 1 of Cycles 5, 7, 9, and so on); additional guidance is provided in Section 7.3.12. Patients who discontinue from treatment prior to documented confirmed PD will be followed for disease progression according to the schedule of assessment until documented confirmed PD.

r. DLT assessment will be done for the Safety Run-in Cohort only and will be assessed through the first 5 weeks of the study; additional guidance is provided in Section 3.2.1.

s. Starting with Cycle 4, TSH and T4 assessments to be performed every 8 weeks (i.e., Day 1 of Cycles 4, 6, 8, and so on).

t. Premedication details are provided in Section 6.1.2.

Table 7-2. Schedule of Assessments (Study Part 1 and Part 2, Dose Level 2)

Cycle	SC	**Priming Cycle 1 (35 days)**								**Cycle 2 (28 days)**				**Cycle 3 (28 days)**		**Cycles 4+ (28 days)**	
Cycle Day	SC	1	2	8	9	11	15	22	29	1	8	15	22	1	15	1	15
Visit Window	-30	None		±1 Day						± 2 Days				± 2 Days		± 2 Days	
Assessments																	
Informed Consent	X																
Demographics	X																
Medical and cancer history	X																
Eligibility criteria	X																
Cohort assignment[a]	X																
Physical examination[b,f]	X	X		X		X	X	X	X	X[b]				X[b]		X[b]	
Vital signs[c]	X	X		X		X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X								X				X		X	
ECG[d]	X	X		X						X							
ECOG performance status[f]	X	X								X				X		X	
Pregnancy test[e,f]	X	X								X				X		X	
Serum chemistry[f]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
CBC, differential, platelets, reticulocytes[f]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Peripheral blood smear[f,g]		X	X	X			X		X	X				X			
Serum uric acid, phosphorous[f]	X	X	X	X		X	X	X	X								
Haptoglobin, D-dimer, thrombin time, plasma fibrinogen[f]	X		X	X		X	X	X	X	X				X		X	
PT/INR, aPTT[f]	X			X						X				X		X	
ACTH, FSH, TSH[f]	X			X								X				X[s]	
T3 (Total), T4 (Free)[f]	X			X								X				X[s]	
ABO/Rh, DAT[f,h]	X																
Urinalysis[f]	X						X	X									

Cycle	SC	**Priming Cycle 1 (35 days)**								**Cycle 2 (28 days)**				**Cycle 3 (28 days)**		**Cycles 4+ (28 days)**	
Cycle Day	SC	1	2	8	9	11	15	22	29	1	8	15	22	1	15	1	15
Visit Window	-30	None		±1 Day						± 2 Days				± 2 Days		± 2 Days	
Assessments																	
Pharmacokinetics[i]		X	X	X	X			X		X		X		X		Q3 cycles See Table 7-4	
CCI																	
Antidrug antibodies[f,l]		X								X				X		Q3 cycles	
Tumor biopsy[m]	X													X			
Tumor markers, if applicable[n]	X[n]									X				X		X[n]	
Response assessment[o]	X[p]													X[q]		Q2C odd cycle[q]	
DLT assessment[r]										X							
Adverse events	→																
Concomitant medications	→																
Hu5F9-G4 premedication[t]		X		X		X											
Hu5F9-G4 administration		X[a]		X		X	X	X	X	X	X	X	X	X	X	X	X
Avelumab premedication[t]				X				X		X		X					
Avelumab administration				X				X		X		X		X	X	X	X

Abbreviations: 1st = first; ABO = any of the four blood groups A, B, AB, and O comprising the ABO system; ADAs = anti-drug antibodies; aPTT = activated partial thromboplastin time; CBC = complete blood count; DAT = direct antiglobulin test; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; INR = international normalized ratio; PE = physical examination; PT = prothrombin time; Rh = Rhesus factor; RO = receptor occupancy; SC = screening; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone.

Footnotes:

a. First dose of Hu5F9-G4 (priming dose) must be given within 30 days of consent.
b. Full PE is required at Screening, a symptom-directed PE is acceptable thereafter; height should be recorded during Screening only; weight should be recorded during Screening and on Day 1 of each cycle.
c. Prior to infusion and within 30 minutes after each infusion (if applicable); vital signs should include heart rate, respiratory rate, blood pressure, and temperature. Height should be recorded during Screening only. Weight should be recorded at Screening and D1 of each Cycle only.
d. A single ECG will be performed at Screening. Triplicate ECGs will be performed at the visits indicated after Screening, within 2 hours prior to avelumab infusion if applicable, and within 30 minutes of the end of Hu5F9-G4 infusion; additional guidance is provided in Section 7.3.2.
e. A urine or serum pregnancy test is 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) 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 performed within the 72 hours prior to dosing. After Screening, all pregnancy tests can be urine or serum pregnancy tests and should be performed on Day 1 of every cycle; additional guidance is provided in Section 7.3.5. Contraceptive requirements for female patients are outlined in Section 4.6.1, and for male patients in Section 4.6.2.
f. Pre-infusion assessments may be performed up to 72 hours before study drug treatment. Most laboratory assessments will be performed locally at each study center's laboratory by means of their established methods; analytes to be assessed by the local laboratory or specialty laboratories are presented in Table 7-5.
g. Peripheral blood smear slides from Cycle 1 will be retained and sent to the Sponsor for storage. Collection guidelines are provided in Section 7.3.6.3. Peripheral blood smears are also to be collected 1 hour (± 30 minutes) after completion of any blood transfusion.
h. Type and screen; additional guidance is provided in Section 7.3.6.7 and Table 7-5.
i. Refer to Table 7-4 for PK time point details; samples should be drawn on the contralateral arm from where the study drugs are being infused and they should not be drawn from central lines where the relevant study drugs have been previously infused; additional guidance is provided in Section 7.3.8.

CCI [redacted]

k. Not applicable.
l. ADAs to Hu5F9-G4 CCI [redacted] should be assessed on Day 1 of Cycles 1, 2, 3, and 4 and then every 3 cycles until Cycle 13, at the End of Treatment Visit, and at the 30-day Safety Follow-up Visit. Additional guidance is provided in Section 7.3.10.
m. Biopsies are to be collected during the Screening Period prior to first dose and on Cycle 3 Day 1 (± 2 weeks); tumor biopsies are CCI [redacted] mandatory for Part 2 where medically feasible. CCI [redacted]
n. Tumor markers should be obtained at Screening. If applicable, they should also be obtained on Day 1 of Cycles 2, 3, and 4. From Cycle 5 and onward, they may be obtained every 2 cycles; additional guidance is provided in Section 7.3.12.
o. After Cycle 3, the adjustment window is ± 2 weeks to coordinate with treatment cycles; additional guidance is provided in Section 7.3.12.
p. Historic imaging may be used for Screening diagnostic imaging if performed within 30 days of the first dose of Hu5F9-G4; additional guidance is provided in Section 7.3.12.

Footnotes:

q. Efficacy assessment should be conducted at ± 1 week of the Cycle 3 Day 1 visit, and then at ± 2 weeks of the Day 1 visit of every other subsequent cycle (i.e., Day 1 of Cycles 5, 7, 9, and so on); additional guidance is provided in Section 7.3.12. Patients who discontinue from treatment prior to documented confirmed PD will be followed for disease progression according to the schedule of assessment until documented confirmed PD.

r. DLT assessment will be done for the Safety Run-in Cohort only and will be assessed through the first 5 weeks of the study; additional guidance is provided in Section 3.2.1.

s. Starting with Cycle 4, TSH and T4 assessments to be performed every 8 weeks (i.e., Day 1 of Cycles 4, 6, 8, and so on).

t. Premedication details are provided in Section 6.1.2.

Table 7-3. Schedule of Assessments for Follow-up (Study Part 1 and Part 2, All Dose Levels)

Assessments	End of Treatment	Safety Follow-up Visit	Safety Follow-up Contact	Long-term Follow-up	Survival Follow-up
	Within 14 days of EOT decision	30 days after last dose of study drug	90 days after last dose of study drug	Every 8 weeks until PD or new anti-cancer therapy	Up to 60 months from LPE
Visit Window		± 1 Week	± 5 Days	± 2 Weeks	± 1 Month
Physical examination (symptom directed)		X			
Vital signs		X			
Weight		X			
ECOG performance status (Appendix D)		X			
Serum or urine pregnancy test[a]		X			
Serum chemistry		X			
CBC with differential, platelets, reticulocytes		X			
TSH, T3 (Total), T4 (Free)		X			
Pharmacokinetics for Hu5F9-G4 and avelumab	X	X			
CCI					
Antidrug antibodies	X	X			
CCI					
Tumor markers, if applicable		X[c]		Q8W	
Response assessment[c]	X[c]	X[c]		Q8W	
Adverse events	X	X	X[d]	Q4W[e]	
Concomitant medications	X	X			
Survival follow-up and new anti-cancer therapy			X[d]		Q3 Months

Abbreviations: AE = adverse event; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; LPE = last patient enrolled;

PD = progressive disease; Q3 = every 3; Q4W = every 4 weeks; Q8W = once every 8 weeks; Q3 months = once every 3 months; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone.

Footnotes:

a. Contraceptive requirements for female patients are outlined in Section 4.6.1, and for male patients in Section 4.6.2.

CCI [redacted]

c. Response assessment is required only if not completed within the 4 weeks prior to the Safety Follow-up Visit. EOT response assessment is required only if not completed within the 4 weeks prior to the EOT Visit. Additional guidance is provided in Section 7.3.12.

d. Safety follow-up contact is to be by phone. Patients who develop study drug-related AEs or SAEs within the 90-day period will be seen by the study physician.

e. Any ongoing SAEs and study drug-related AEs and new SAEs reported after the AE collection period (i.e., assessed as study drug-related should be followed every 4 weeks until resolution or return to baseline; stabilization of the event; the patient is lost to follow-up, withdraws consent, or starts another anti-cancer therapy; or when the Medical Monitor deems it necessary, whichever occurs first.

Table 7-4. Blood Sampling Times for PK CCI [redacted] (Study Part 1 and Part 2)

Time Points	Cycle									EOT	SFU
	1					2		3	4+		
Day	**1**	**2**	**8**	**9**	**22**	**1**	**15**	**1**	**1**	**Variable**	**Variable**
PK (Hu5F9-G4 and avelumab)											
Pre-study drug infusion (within 12 hours)	X				X	X[a]	X	X[a]	X[a,b]	X[e]	X
1 hour (±15 minutes) after Hu5F9-G4 infusion	X		X								
24 hours (±15 minutes) after Hu5F9-G4 infusion, Part 1 only		X		X							
CCI [redacted]											

Abbreviations: C = cycle; EOT = End of Treatment; PD = progressive disease; PK = pharmacokinetics; SFU = Safety Follow-up.

a. Hu5F9-G4 sample may be collected before the avelumab infusion at same time as the "pre-avelumab infusion" PK time point.

b. Starting with Cycle 4, samples are to be collected every third cycle until Cycle 13, and then the End of Treatment Visit.

CCI [redacted]

e. Obtained at the time of PD, or the start of a new anticancer therapy. EOT sample to be collected only if the visit occurs prior to Cycle 2.

7.2. Screening Assessments

Refer to the schedule provided in Table 7-1 for specific timing of screening procedures.

The patient must be willing and able to sign and date the ICF before any Screening assessments or study-specific tests may be performed. All patients who are enrolled will be given a unique study number that will be used to identify the patient throughout the study.

Screening assessments will be completed within a 30-day Screening Period prior to the first dose of study drug. Screening assessments may be repeated during the 30-day Screening period. Screening assessments may be used for pre-infusion assessments on 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 required Screening period. The first dose of Hu5F9-G4 (priming dose) and must be given within 30 days of all Screening assessments.

7.3. Study Procedures

Refer to the schedules provided in Table 7-1, Table 7-2, Table 7-3, and Table 7-4 for specific timing of study procedures.

7.3.1. Physical Examination

Physical examinations will be assessed in accordance with the schedules provided in Section 7 (Table 7-1, Table 7-2, and Table 7-3). A complete physical examination should be performed at Screening. Thereafter, symptom-directed physical examinations are acceptable. Changes from baseline abnormalities should be recorded in the patient's study source documents. New or worsened abnormalities should be recorded as AEs on the Adverse Event Case Report Form (CRF).

Height should be recorded during Screening only; weight should be recorded during Screening and on Day 1 of each cycle. Refer to Section 6.1.1 for guidelines regarding weight-based dosing for Hu5F9-G4.

7.3.2. Vital Signs

Vital signs will be assessed in accordance with the schedules provided in Section 7 (Table 7-1, Table 7-2, and Table 7-3). Vital signs should include heart rate, respiratory rate, blood pressure, and temperature, and weight.

7.3.3. Electrocardiograms

Electrocardiograms (ECGs) will be assessed in all patients in accordance with the schedule provided in Table 7-1. One ECG will be performed at Screening. Triplicate ECGs will be performed at the visits indicated after Screening.
If applicable, the triplicate ECGs should be performed within 2 hours prior to the first infusion (i.e., Hu5F9-G4 on C1D1, avelumab on C1D8 and C2D1) and within 30 minutes of the end of Hu5F9-G4 infusion on treatment. The interval between ECG reads will be according to the Institution's standard of care.

7.3.4. Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed in all patients in accordance with the schedules provided in Section 7 (Table 7-1, Table 7-2, and Table 7-3). The ECOG performance status scale is provided in Appendix D.

The ECOG performance status is a scale used to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

7.3.5. Pregnancy Test

Pregnancy tests will be performed in accordance with the schedules provided in Section 7 (Table 7-1, Table 7-2). Pregnancy tests are required only for women of childbearing potential. Note that a woman is considered to be of childbearing potential (WOCBP), i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the

postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. A urine or serum pregnancy test is required at Screening and within 72 hours before study drug administration on Day 1. The Day 1 pregnancy test does not need to be repeated if the Screening pregnancy test was performed within the 72 hours before study drug administration. Pregnancy tests will be performed every 4 weeks, starting with Cycle 2.

7.3.6. Laboratory Tests

Laboratory assessments will be performed in accordance with the schedules provided in Section 7 (Table 7-1, Table 7-2, and Table 7-3). Most laboratory assessments will be performed locally at each study center's laboratory by means of their established methods; analytes to be assessed by the local laboratory or specialty laboratories are presented in Table 7-5. Before starting the study, the Investigator will provide the Sponsor (or designee) with a list of the normal ranges and units of measurement. Pre-infusion assessments may be performed up to 72 hours before study drug treatment.

Table 7-5. 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 Phosphorus Total bilirubin Direct bilirubin LDH AST (SGOT) ALT (SGPT) Alkaline phosphatase	RBC Hemoglobin Hematocrit Platelets WBC Differential • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes Reticulocytes Haptoglobin D-Dimer Thrombin Plasma fibrinogen PT, aPTT, and INR Peripheral Blood Smear • Spherocytes • RBC Fragments/Schistocytes • RBC Agglutination • Nucleated RBCs • RBC abnormalities • Platelet Aggregation	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 [redacted] Pharmacokinetics [a] ADAs [a] ACTH/FSH/TSH/ T3 (Total)/T4 (Free)

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; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cells.
Note: Refer to Section 7.1 Schedule of Assessment tables for collection time points.
a. These assays may be performed at a specialty laboratory.

7.3.6.1. Serum Chemistry

Serum chemistries will be assessed at the time points outlined in the schedules provided in Section 7 (Table 7-1, Table 7-2, and Table 7-3). Analytes to be assessed by the local laboratory or specialty laboratories are presented in Table 7-5.

7.3.6.2. Complete Blood Count with Differential

CBC with differential will be assessed at the time points outlined in the schedules provided in Section 7 (Table 7-1, Table 7-2, and Table 7-3). CBC will include WBC count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), RBC count, platelet count, hemoglobin, and hematocrit. Specific hematology tests to be assessed by the local laboratory or specialty laboratories are presented in Table 7-5.

7.3.6.3. Peripheral Blood Smear Assessment

Peripheral smears will be collected at selected time points as outlined in the schedule provided in Table 7-1 and Table 7-2, and assessed for the presence of hemagglutination, in addition to standard cell morphology assessment. Slides should be processed and assessments occur in accordance with your local practice. These samples should be collected from the arm contralateral to the arm being used for drug infusion, if possible. Whenever 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. CCI [redacted]

7.3.6.4. Serum Uric Acid and Phosphorus

Serum uric acid and phosphorus tests will be performed at the time points outlined in the schedule provided in Table 7-1 and Table 7-2.

7.3.6.5. Haptoglobin, D-dimer, Thrombin Time, and Plasma Fibrinogen

Haptoglobin, D-dimer, thrombin time, and plasma fibrinogen tests will be performed at the time points outlined in the schedule provided in Table 7-1 and Table 7-2.

7.3.6.6. Prothrombin Time/ International Normalized Ratio, Activated Partial Thromboplastin Time

Prothrombin time/ international normalized ratio, and activated partial thromboplastin time (PT/INR, aPTT) will be assessed at the time points outlined in the schedule provided in Table 7-1 and Table 7-2.

7.3.6.7. Type and Screen (ABO/Rh), Direct Antiglobulin Test

Due to the risk of developing anemia, blood phenotyping, type and screen (ABO/Rh), and DAT should be performed at Screening prior to exposure to Hu5F9-G4: Full phenotyping (if not transfused in last 3 months) should include ABO, Rh, D, C, E, Kell, Kidd, Duffy, MNS, and antibody screen tests. (The complete list of analytes is presented in Table 7-5.) 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.

7.3.7. Urinalysis

Urinalysis will be assessed at the time points outlined in the schedule provided in Table 7-1 and Table 7-2. Urinalysis will include dipstick results for color, appearance, specific gravity, pH, RBCs, glucose, bilirubin, ketones, occult blood, and protein.

7.3.8. Pharmacokinetic Assessments

Serum samples for PK analysis will be collected according to the schedules provided in Section 7 (Table 7-1, Table 7-2, Table 7-3, and Table 7-4). PK samples will be collected to assess the PK of Hu5F9-G4 and to explore the kinetics of avelumab. PK samples will be sent to a central lab for processing. The exact date and time of

each PK sampling should be recorded, as well as the exact date and time of the beginning and end of each infusion of Hu5F9-G4 and avelumab. Samples should be drawn on the contralateral arm from where the study drugs are being infused and they should not be drawn from central lines where the relevant study drugs have been previously infused.

7.3.9. CCI [redacted] Biomarker Assessments

CCI [redacted]

7.3.10. Anti-drug Antibodies

ADAs will be tested according to the schedules provided in Section 7 (Table 7-1, Table 7-2, and Table 7-3). As shown in the SOA Table 7-1 and Table 7-2, peripheral blood for immunogenicity assessments for ADAs against Hu5F9-G4 CCI [redacted] will be collected on Days 1, and then on Day 1 of Cycles 2 to 4, and every 3 cycles thereafter to coincide with tumor response assessments, and as shown in Table 7-3, at the End of Treatment and Safety Follow-up Visits. When collected on the day of study drug dosing, the blood sample must be collected before dose administration. A validated tiered testing process (screening+confirmation+titre) will be used to measure antibodies to Hu5F9-G4 in serum samples. For patients who have tested positive for ADAs, the impact of ADAs on PK, safety, and biologic activity may be assessed, if relevant. CCI [redacted]

7.3.11. Tumor Biopsies

Biopsies will be collected according to the schedules provided in Section 7 (Table 7-1, Table 7-2, and Table 7-3). Tumor biopsies will be used to explore the effects of Hu5F9-G4 and avelumab on the tumor microenvironment, including but not limited to, the possible evaluation of the types of immune cells present and the expression of CD47 and other relevant markers. In addition, PD-L1 expression will be evaluated on tumor cells and/or immune cells by immunohistochemistry. These tumor biopsies are CCI [redacted] mandatory in Part 2, unless the Investigator and Sponsor determine that, in particular cases, obtaining a tumor biopsy 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 collected during the Screening Period prior to first dose and on Cycle 3 Day 1 (± 2 weeks). Core biopsies may be collected for these time points; however excisional biopsies, where possible, are preferred over core biopsies. Fine needle aspiration biopsies are not acceptable. Biopsies should ideally contain 30% or ≥100 viable tumor cells.

CCI [redacted]

7.3.12. Response Assessments

Response assessments will be collected according to the schedules provided in Section 7 (Table 7-1, Table 7-2, and Table 7-3). Appropriate cancer staging assessments should be performed. Imaging assessments are to be conducted according to RECIST v1.1 (Eisenhauer 2009) and irRECIST (Bohnsack 2014) as described in Section 10.1. The same imaging modality used at Screening should be used throughout the study whenever possible.

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 was performed within the past 4 weeks or a prior response assessment showed documented confirmed PD. Tumor markers should be obtained at Screening (Section 7.3.11). If applicable, they should be obtained on Day 1 of Cycles 2, 3, and 4. From Cycle 5 and onward, they may be obtained every 2 cycles.

7.3.13. Adverse Events

Adverse events will be recorded according to the schedules provided in Section 7 (Table 7-1, Table 7-2, Table 7-3, and Table 7-4). After signing informed consent, all SAEs will be collected regardless of attribution (Section 9.2.1). At each visit all AEs observed by the Investigator or reported by the patient that occur after the first dose of study drug through 30 days after the last dose of study drug are to be reported using the applicable electronic case report form (eCRF; Section 9.3.1). AEs that occur prior to 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 study drug, Investigators are to report any new study drug-related SAEs that occur up to 90 days after the last dose or the start of new anti-cancer treatment (whichever occurs first), any ongoing SAEs, and study drug-related AEs, including late-onset immune-mediated AEs. At any time, any new SAEs assessed by the Investigator as related to Hu5F9-G4 and/or avelumab must be reported. Patients who develop study drug-related AEs or SAEs within the 90-day period will be seen by the study physician.

7.3.14. Concomitant Medications

Concomitant medications will be recorded according to the schedules provided in Section 7 (Table 7-1, Table 7-2, Table 7-3, and Table 7-4). 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 eCRF.

7.3.15. End of Treatment Visit

The End of Treatment (EOT) Visit to be completed within 14 days of the decision to end treatment with either or both study drugs. Refer to the schedule provided in Table 7-3 for specific EOT study procedures.

7.3.16. Safety Follow-up

The Safety Follow-up Visit is to be completed within 30 days (± 1 week) after the last dose of the last study drug received. Refer to the schedule provided in Table 7-3 for specific Safety Follow-up Visit procedures. Patients will be followed until PD or until they begin a new anti-cancer therapy. For patients who achieve a PR or CR while on study, a repeat disease assessment will be obtained at the time of PD whenever possible. CCI

The Safety Follow-up Contact is to be completed by phone 90 days (± 5 days) after the last dose of last study drug received. The call will collect information on new study drug-related SAEs, ongoing SAEs, and study drug-related non-serious AEs, including late-onset immune-mediated AEs. At any time, any new SAEs assessed by the Investigator as related to Hu5F9-G4 and/or avelumab must be reported. Patients who develop study drug-related AEs or SAEs within the 90-day period will be seen by the study physician.

7.3.17. Long-term Follow-up

After the Safety Follow-up Contact (90 days after last dose), patients will be followed for any ongoing SAEs and study drug-related AEs and new SAEs assessed as related to study drug every 4 weeks until resolution to baseline, stabilization, until the patient starts a new anti-cancer therapy, or the patient is lost to follow-up, whichever occurs first. Any SAE assessed as related to study drug must be reported whenever it occurs, irrespective of the time elapsed since the last administration of study drug. Patients will also be asked about any anti-cancer therapy. For patients without

documentation of disease progression, long-term follow-up will occur every 8 weeks until disease progression or the patient begins a new anti-cancer therapy.

7.3.18. Survival Follow-up

Survival will be assessed in accordance with the schedule provided in Table 7-3. All patients who permanently discontinue all study treatment will be contacted during a clinic visit or by telephone to assess the following:

- Survival
- Disease progression (if not documented previously)
- Commencement of new cancer therapy following the last administration of study drug

Patients will be contacted every 3 months (± 1 month) from the date of the Safety Follow-up Contact, until 60 months from the date that the last patient is enrolled into the study or full withdrawal of consent until death or study closure, whichever occurs first. For any patient who dies during this period, the date and 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.

8. STUDY DISCONTINUATION

8.1. Withdrawal of Patients from Study Drug Treatment

Patients (or a legally acceptable representative) may decline to continue receiving study drug at any time during the study. The patient's health and welfare is the primary consideration in any determination to discontinue study drug treatment. Patients who withdraw from study drug during the treatment period should be encouraged to return for an EOT Visit for evaluation of safety within 2 weeks of the decision to end Hu5F9-G4 + avelumab combination treatment. The studies to be performed at this visit are listed in Schedule of Assessments Table 7-3. It is strongly encouraged that patients return for their Safety Follow-up Visit 30 days (± 1 week) after their last dose of study drug. The assessments to be performed at this visit are

described in Table 7-3. All patients who withdraw from study drug treatment will be followed for disease response and survival.

Reasons for withdrawal from study drug treatment may include, but are not limited to:

- Confirmed tumor progression according to irRECIST.
- Unacceptable toxicity.
- Clinically significant change in the patient's status that precludes further treatment (e.g., pregnancy or other AE), after discussion with the Medical Monitor.
- Patient's request, with or without a stated reason. In case the patient decides to withdraw from treatment, further study assessments should be performed unless declined by the patient.
- Investigator or treating physician decision in the absence of any of the above.
- Pregnancy.

8.2. Withdrawal of Patients from Study

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

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

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

8.3. Defining the End of Study

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 the last visit (phone contact is also considered as a visit) or when the CTSC decides to terminate 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 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.
- Sponsor decision.

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

8.4. Study Termination

The Sponsor reserves the right to terminate the study at any time. Both the Sponsor 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 the Investigator's termination of participation in the study and send a copy of the notification to the Sponsor.

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; and the results from other protocol-specified tests that are deemed critical to the safety evaluation of the combination of these study drugs.

The Sponsor, or its designee, is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating Investigators, in accordance with International Conference on Harmonisation (ICH) guidelines, 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), including AEs that occur prior to study drug treatment that are related to protocol-mandated interventions.
- Events that occur prior to administration of both study drugs that are related to a protocol-mandated intervention (e.g., invasive procedures such as biopsies)
- Pre-existing 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 study drug(s)
- Considered a significant medical event by the Investigator based on sound medical and scientific judgment (i.e., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

After initiation of any of the study drugs, all AEs and SAEs, regardless of attribution, will be collected until 30 days following the last administration of last study drug received, or until the Safety Follow-up Visit (whichever occurs later) unless the patient begins a new anti-cancer therapy before that. Until 90 days after the last dose of last study drug received or the Safety Follow-up Contact (whichever occurs later), Investigators are to report only new study drug-related AEs or SAEs, (including late-onset immune-mediated AEs). Patients who develop study drug-related AEs or SAEs within the 90-day period will be seen by the study physician. Follow-up information regarding SAEs and study drug-related AEs will be reported until resolution (or return to baseline), stabilization of the event, the patient is lost to follow-up or withdraws consent, the Medical Monitor deems it necessary, or the patient initiates new anti-cancer therapy, whichever occurs first. Follow-up will be conducted as described in Section 7.3.16 and Section 7.3.17. Resolution of AEs and SAEs (with dates) should be documented on the Adverse Event eCRF, on the SAE Report Form (if applicable), and in the patient's medical record to facilitate source data verification. 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 any of the study drugs (Hu5F9-G4 and/or avelumab received as part of this study).

9.2.2. Eliciting Adverse Events

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

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

9.2.3. Assessment of Severity and Causality of Adverse Events

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

For each AE and SAE, the Investigator will make an assessment of seriousness (Section 9.1.2), severity (Table 9-1), and causality (Table 9-2). A causality assessment will be made for both Hu5F9-G4 and avelumab individually. Table 9-2 provides guidance for assessing the causal relationship to study drug(s).

The AE grading (severity) scale NCI CTCAE Version 4.03 (Appendix C) will be used for AE reporting as shown in Table 9-1. As described in Section 6.5 (Safety Management Guidelines), customized severity grading for hemagglutination and microangiopathy AEs will be used (Appendix C).

Table 9-1. 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 C)
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 for either study drug, Investigators should apply the following general guidelines (Table 9-2).

Table 9-2. Causal Attribution Guidance

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

Abbreviations: AE = adverse event; SAE = serious adverse event.
Note: The Investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Related" or "Not Related" causality assessment for individual AE reports, the Sponsor 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 and concepts when recording AEs and SAEs. Colloquialisms and abbreviations are to be avoided.

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

9.3.1.2. Adverse Events Occurring Secondary to Other Events

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

9.3.1.3. Persistent or Recurrent Adverse Events

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

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

9.3.1.4. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities will be recorded as AEs on the eCRF (e.g., abnormalities that require study drug 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 $\times$ ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to 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 SAE Report Form and 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, especially in the absence of other signs and symptoms, record "[specific disease 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 be routinely 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 can be recorded as an SAE, if the outcome is fatal in the absence of other signs and symptoms, or if the Investigator assesses the PD 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 specifically instructed otherwise in this protocol.

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

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a pre-existing 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. The following sections describe such information.

9.3.1.8.1. Pregnancy

Female patients who become pregnant during the treatment period must be withdrawn from study treatment immediately.

Any pregnancy occurring in a patient or a patient's partner during treatment with either study drug or within 6 months of last study drug administration must be reported to the Sponsor's safety clinical research organization (CRO) (Section 9.2) within 24 hours of becoming aware of it, using a Pregnancy Notification Form (provided in the Investigator Trial File). It is the Investigator's responsibility to obtain consent for follow-up from the patient or patient's partner. The safety CRO will follow-up on all pregnancies for the pregnancy outcome through the Investigator, using a Pregnancy Outcome Form. Data will be collected about the pregnancy, fetal

status, neonate status. In the event that the neonate has abnormalities at birth, additional data will be collected for the infant about those abnormalities. 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 9.2. 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 also be recorded and reported as an SAE within 24 hours of awareness.

9.3.1.8.2. Overdose

An overdose of Hu5F9-G4 is defined as a dose higher than that indicated in the protocol, with or without experiencing an AE.

An overdose of avelumab is defined as any dose ≥10% than the planned dose for that particular administration.

Any overdose must be recorded in the trial drug section of the eCRF.

9.3.1.8.3. Abuse or Misuse

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

9.4. Reporting Requirements for Serious Adverse Events

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

Medical Monitor Contact Information for Sites:

PPD
Telephone No.: PPD
Alternate Telephone No.: PPD
Email: PPD

Alternate Medical Monitor Contact Information for Sites:

PPD

Telephone No.: PPD

Alternate Telephone No.: PPD

Email: PPD

10. MEASUREMENT OF EFFECT

10.1. Anti-Cancer Effect

Patients will be assessed for response using RECIST v1.1 (Eisenhauer 2009) for the primary efficacy endpoint and irRECIST (Bohnsack 2014) for the secondary efficacy endpoint. The first response assessment will occur after 2 cycles of treatment. Subsequent response assessments will occur every 2 cycles or approximately 8 weeks. Tumor markers will be obtained, as appropriate, at baseline, and then every cycle until Cycle 5, then every 2 cycles. Finally, response assessment will be obtained at the EOT Visit, unless a prior radiographic assessment has been performed within the last 4 weeks or a prior response assessment documented confirmed PD.

11. STATISTICAL CONSIDERATIONS

The primary objectives of this Phase 1b study are to describe the safety and tolerability of the combination of Hu5F9-G4 and avelumab and determine the recommended Phase 2 dose and schedule (RP2DS). As such, the statistical analysis will be primarily descriptive providing listings, graphic displays, frequencies, and/or percentages for discrete variables and the mean, standard deviation, median, and ranges for continuous variables. Where relevant, 95% confidence intervals (CIs) may also be provided. Time-to-event endpoints will be summarized using Kaplan-Meier methods.

11.1. Analysis Sets

11.1.1. Part 1 Safety Run-In Cohort

Dose Evaluation Set (DES)

The Dose Evaluation Set includes all enrolled solid tumor patients in Part 1 who receive at least 1 dose of both Hu5F9-G4 (at a maintenance level) and avelumab and either experience a DLT or complete at least 4 infusions of Hu5F9-G4 (at the maintenance level) and 2 infusions of avelumab.

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

11.1.2. Parts 1 and 2 Safety and Efficacy Analysis Cohort

Efficacy Analysis Set (EAS)

The Efficacy Analysis Set (EAS) includes all enrolled patients who receive at least 4 doses of Hu5F9-G4 (at the maintenance level) and 2 doses of avelumab, and for whom a baseline and post-treatment tumor assessment is available.

The analysis of overall response rate (ORR), best overall response (BOR), duration of response (DOR), time to tumor progression (TTP), PFS, and OS will be performed on the EAS.

Safety Analysis Set (SAS)

The Safety Analysis Set (SAS) includes all enrolled patients who receive at least 1 dose of either study drug. The analysis of safety will be performed on the SAS.

PK Analysis Set (PAS)

The PK Analysis Set (PAS) includes all patients in the SAS from whom PK blood samples are collected during the study and who have at least one measurable concentration of Hu5F9-G4.

11.2. Sample Size Determination

This trial will include a total of up to 40 patients. This sample size includes both Parts 1 and 2 of the study, allowing for patient replacement as defined in this protocol. In Part 1, up to 12-18 patients will be treated in a Safety Run-in Cohort, assuming that no more than 2 DLTs in each cohort of 6 patients occur. Up to 18 patients may be enrolled in Part 1 if some patients are ineligible for DLT assessment.

Part 2 consists of a single expansion cohort in 20 ovarian cancer patients who will undergo safety, PK, CCI [redacted]. This sample size will allow for confirmation of the safety profile of Hu5F9-G4 and avelumab in this population, and the mandatory tumor biopsies CCI [redacted] The anti-tumor activity of this regimen will also be documented. With this sample size, the lower bound of the 95% exact CI would exclude 10% if the objective response rate is 30% or higher.

11.3. 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 Part 2 CCI [redacted]. The CTSC will meet at a minimum at the completion of the DLT period for each cohort in the Safety Run-in part 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.

11.4. Data Monitoring Committee

Data Monitoring Committee functions for this trial will be performed by the CTSC, as defined and described in Section 11.3.

11.5. 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.

11.6. Statistical Methods

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

All analyses will be conducted separately for patients in Parts 1 and 2 of the study unless otherwise specified. Safety analyses may be conducted for patients in both Parts 1 and 2 of the study together. Efficacy analyses may also be conducted on all efficacy-evaluable ovarian cancer patients.

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

11.6.1. Efficacy Analyses

The efficacy analyses will be conducted for patients in the EAS, unless otherwise indicated. The EAS will be used to analyze the outcome measures described in the table below.

Measure	Definition
ORR	The proportion of patients who achieve a complete or partial response according to RECIST v1.1 (primary endpoint) or irRECIST (secondary endpoint).
DOR	Time from the initial response until confirmed tumor progression.
TTP	The length of time from first dose of treatment combination to confirmed tumor progression.
PFS	Time from first dose of treatment combination to confirmed tumor progression or death, whichever occurs first.
OS	Time from first dose of treatment combination until death.

ORR will be summarized by frequency and percentages along with 95% exact CI. The time-to-event endpoints of DOR, TTP, PFS, and OS will be summarized using Kaplan-Meier methods. Additional details will be provided in the SAP.

11.6.2. Safety Analyses

The SAS is defined as all patients who receive at least 1 dose of study drug (either Hu5F9-G4 or avelumab). 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 for patients in Part 1, TEAEs (AEs worsening or occurring during or after a patient's first exposure to study drug), study drug-related adverse events (ADRs), vital signs, physical examinations, laboratory, CD47 RO, and ADA assessments. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 19.0) and grouped by system organ class and preferred term. Summary tables will include the number and percentage of patients with AEs, SAEs, fatal AEs, and other AEs of interest.

Data will be presented by Part 1 (Safety Run-in Cohort) and by Part 2 (Ovarian Cancer Expansion Cohort), and, 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.

11.6.2.1. Adverse Events

For the SAS, AEs that occurred during Screening, but before exposure to study drug will be reported in the AE line listings and appropriately identified as non-TEAEs. Summary tables of TEAEs and ADRs 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 and ADRs will also be tabulated using Investigator assessment of the relationship to study drug (related or not related). SAEs, including deaths, will be summarized and/or listed for each dose cohort and for all dose cohorts combined. TEAEs and ADRs resulting in withdrawal from study drug 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.

For patients who went through Screening only or who were enrolled but never treated, AEs and SAEs that occur during Screening will be reported separately as the "Screened-only/Never Treated" Set with line listings and/or summary tables, along with relevant demographic data collected.

11.6.2.2. 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.

11.6.3. Pharmacokinetic Analyses

PK analysis will be conducted for Hu5F9-G4 using the PAS. Based on the distinct MOAs of Hu5F9-G4 and avelumab, drug-drug PK interactions are not expected. Thus, samples for PK analysis for avelumab 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. Due to the sparse sampling regime, it is anticipated that the C_{max} after the first maintenance dose will be the only calculable PK parameter in this population. 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.

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 set to zero in summary statistics, and reported as-is in data listings. Any missing PK parameter data will not be imputed. Population PK modelling analysis may also be conducted by combining Hu5F9-G4 PK data from this study along with data from other studies, but results of that analysis will be reported separately.

CCI [redacted]

11.6.5. Immunogenicity Analyses

The rate and magnitude of anti-Hu5F9-G4 antibody positivity will be evaluated for all patients in Parts 1 and 2 of the trial, and for the pooled patient population. The antibody occurrence rate will be summarized at each time point. Titer summaries by time point may also be provided, if appropriate. CCI [redacted]

CCI [redacted] Immunogenicity analysis may also be performed for avelumab. However, it is not expected that Hu5F9-G4 will impact the immunogenicity of avelumab and vice versa.

11.7. Handling of Missing Data

Details regarding handling missing data will be described in the SAP.

12. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

12.1. Compliance Statement

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

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

12.2. Investigator Responsibilities

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

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

The Investigator or designee must submit to the IRB/IEC any written safety report or update (e.g., amended 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 the Sponsor, will be any or all of the following:

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

12.3. Institutional Review Board or Independent Ethics Committee

A copy of the protocol, proposed ICF, other written patient information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and ICF must be received by the Sponsor 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 the Sponsor, 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 the Sponsor.

12.4. Informed Consent and Human Subject Protection

An initial sample ICF is provided for the Investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Sponsor's 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 patient, to the patient's participation in the clinical study.

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

copy of the signed consent form is to be provided to the patient or legally acceptable representative.

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

12.5. Confidentiality

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

- Subjects are to be identified by a unique patient identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the eCRF demographics page, in addition to the unique patient identification number, the patient's age at time of enrollment is to be included.
- For SAEs reported to the Sponsor, any source documentation provided (e.g., medical records, laboratory results) must have any patient identifier (e.g., patient name, initials, medical records number) fully redacted (i.e., blacked out) prior to transmission.
- Documents that are not submitted to the Sponsor (e.g., signed ICFs) are to be kept in confidence by the Investigator, except as described below.

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

12.6. Urgent Safety Measures

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

The Investigator must inform the Sponsor 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 the Sponsor 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

The Sponsor will comply with ICH GCP guidelines for reporting serious breaches and fraud which may occur in this particular trial in all regions in which the investigational product is being studied.

Investigators must notify the Sponsor immediately if any serious breach of GCP is suspected.

If there is any proof of fraud this must also be reported to the Sponsor. All instances of confirmed clinical trial fraud occurring at sites in the United Kingdom (UK) will be treated according to the procedure for dealing with a serious breach and must be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) within 7 days of the Sponsor becoming aware.

12.8. Study Monitoring

The Sponsor's 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 Sponsor's 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 Sponsor's 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 Sponsor's 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 (as described in Section 7.1), the Investigator may

search publicly available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

The Investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. Data collection will involve the use of the electronic data capture (EDC) system, to which only authorized personnel will have access. The Investigator agrees to maintain accurate eCRFs or paper CRFs and source documentation as part of the case histories. The Sponsor 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 the Sponsor 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.

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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

Blazar BR, Lindberg FP, Ingulli E, et al. CD47 (integrin-associated protein) engagement of dendritic cell and macrophage counterreceptors is required to prevent the clearance of donor lymphohematopoietic cells. J Exp Med 2001;194(4):541-549.

Bohnsack O, Ludajic K, and Hoos A. Adaptation of the immune-related response criteria: irRECIST. Annals of Oncology. 2014;25(4): iv361-iv372.

Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366(26):2455-65

Chao MP, Alizadeh AA, Tang C, et al. Anti-CD47 antibody synergizes with rituximab to promote phagocytosis and eradicate non-Hodgkin lymphoma. Cell. 2010a;142(5):699-713.

Chao MP, Jaiswal S, Weissman-Tsukamoto R, et al. Calreticulin is the dominant pro-phagocytic signal on multiple human cancers and is counterbalanced by CD47. Sci Transl Med. 2010b;2(63):63ra94.

Chao MP, Alizadeh AA, Tang C, et al. Therapeutic antibody targeting of CD47 eliminates human acute lymphoblastic leukemia. Cancer Res. 2011a;71(4):1374-1384.

Chao MP, Tang C, Pachynski RK, et al. Extranodal dissemination of non-Hodgkin lymphoma requires CD47 and is inhibited by anti-CD47 antibody therapy. Blood. 2011b;118(18):4890-4901.

Chao MP, Majeti R, Weissman IL. Programmed cell removal: a new obstacle in the road to developing cancer. Nat Rev Cancer. 2012;12(1):58-67.

Davis A, Tinker AV, Friedlander M. “Platinum resistant” ovarian cancer: What is it, who to treat and how to measure benefit? Gynecol Oncol 2014;133:624-631.

Disis ML, Patel MR, Pant S, et al. Avelumab (MSB0010718C; anti-PD-L1) in patients with recurrent/refractory ovarian cancer from the JAVELIN Solid Tumor phase 1b trial: Safety and clinical activity. J Clin Oncol 34, 2016 (suppl; abstr 5533).

Dong H, Zhu G, Tamada K, Chen L. B7-H1, a third member of the B7 family, co-stimulates T cell proliferation and interleukin-10 secretion. Nat Med 1999;5:1365-69.

Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002; 8:793-800. [Erratum, Nat Med 2002; 8:1039.]

Edris B, Weiskopf K, Volkmer AK, et al. Antibody therapy targeting the CD47 protein is effective in a model of aggressive metastatic leiomyosarcoma. Proc Natl Acad Sci USA. 2012a;109(17):6656-6661.

Edris B, Weiskopf K, Weissman IL, et al. Flipping the script on macrophages in leiomyosarcoma. Oncoimmunology 2012b;1(7):1202-1204.

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(2): 228-247.

Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192:1027-34.

Freshwater T, Kondic A, Ahamadi M, et al. Evaluation of dosing strategy for pembrolizumab for oncology indications. J Immunother Cancer. 2017;5:43.

Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (Anti PD-1) in melanoma. N Engl J Med 2013;369:134-44.

Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014;515:563-567.

Iwai Y, Ishida M, Tanaka Y, et al. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 2002;99:12293-97.

Jaiswal S, Jamieson CH, Pang WW, et al. CD47 is upregulated on circulating hematopoietic stem cells and leukemia cells to avoid phagocytosis. Cell. 2009;138(2):271-285.

Kim D, Wang J, Willingham SB, et al. Anti-CD47 antibodies promote phagocytosis and inhibit the growth of human myeloma cells. Leukemia. 2012;26(12):2538-2545.

Latchman Y, Wood CR, Chernova T, et al. PD-L1 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol 2001;2(3):261-68.

Liu X, Pu Y, Cron K, et al. CD47 blockade triggers T cell-mediated destruction of immunogenic tumors. Nat Med. 2015a;21(10):1209-1215.

Liu J, Wang L, Zhao F, et al. Pre-clinical development of a humanized anti-CD47 antibody with anti-cancer therapeutic potential. PLoS One. 2015b;10(9):e0137345.

Majeti R, Chao MP, Alizadeh AA, et al. CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. Cell. 2009;138(2):286-299.

Okazawa H, Motegi S, Ohyama N, et al. Negative regulation of phagocytosis in macrophages by the CD47-SHPS-1 system. J Immunol 2005;174(4):2004-2011.

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.

Oldenborg PA, Zheleznyak A, Fang YF, et al. Role of CD47 as a marker of self on red blood cells. Science 2000;288(5473):2051-2054.

Pollard JW. Tumour-educated macrophages promote tumour progression and metastasis. Nature Rev Cancer. 2004;4:71-78.

Rustin GJ, Vergote I, Eisenhauer E, et al. Gynecological Cancer Intergroup. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer. 2011 Feb;21(2):419-23.

Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1 (PD-L1) pathway to activate anti-tumor immunity. Curr Opin Immunol 2012a;24:207-12.

Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012b;366(26):2443-54.

Tseng D, Volkmer JP, Willingham SB, et al. Anti-CD47 antibody-mediated phagocytosis of cancer by macrophages primes an effective antitumor T-cell response. Proc Natl Acad Sci USA. 2013;110(27):11103-11108.

Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014;515:568-571.

Wang DD, Zhang S, Zhao H, et al. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009;49(9):1012-24.

Willingham SB, Volkmer JP, Gentles AJ, et al. The CD47-signal regulatory protein alpha (SIRPα) interaction is a therapeutic target for human solid tumors. Proc Natl Acad Sci USA. 2012;109(17):6662-6667.

Zhang M, Hutter G, Kahn S, et al. Anti-CD47 treatment stimulates phagocytosis of glioblastoma by M1 and M2 polarized macrophages and promotes M1 polarized macrophages in vivo. PLoS One. 2016;11(4):e0153550.

Zhao X, Suryawanshi S, Hruska M, et al. Assessment of nivolumab benefit-risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors. Ann Oncol. 2017;28(8):2002-2008.

14. APPENDICES

Appendix A. Avelumab Study Information for JAVELIN 100

JAVELIN 100 Study Title: A Randomized, Open-label, Multicenter, Phase 3 Study To Evaluate The Efficacy And Safety Of Avelumab (msb0010718c) In Combination With And/or Following Chemotherapy In Patients With Previously Untreated Epithelial Ovarian Cancer Javelin Ovarian 100

Available online:
https://clinicaltrials.gov/ct2/show/NCT02718417?term=JAVELIN&cond=Ovarian+Cancer&rank=1

Accessed 6 April 2018

Appendix B. Avelumab Prescribing Information

Avelumab (BAVENCIO®) Prescribing Information (3/2017 Version)

Available online:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761049s000lbl.pdf

Accessed 30 January 2018

Appendix C. 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_5x7.pdf

Accessed 23 July 2018

Appendix D. Eastern Cooperative Oncology Group Performance Status

Table 14-1. Eastern Cooperative Oncology Group Performance Status

Grade	Performance Status Criteria
0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light sedentary nature (light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

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.

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 adapted from 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.